

**Report of
the Committee of Inquiry
on the Case Involving
Dr. Nancy Olivieri,
the Hospital for Sick Children,
the University of Toronto,
and Apotex Inc.**

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Key to Abbreviations

ADR	adverse drug reactions
ASH	American Society of Hematology (U.S.)
CAUT	Canadian Association of University Teachers
CFI	Canada Foundation for Innovation
CIBC	Canadian Imperial Bank of Commerce
CIHR	Canadian Institutes for Health Research
CMPA	Canadian Medical Protective Association
CoI	the present Committee of Inquiry
CPSO	College of Physicians and Surgeons of Ontario
DFO	deferoxamine
EAP	Expert Advisory Panel
EDR	Emergency Drug Release (programme of the HPB)
EMA	European Agency for the Evaluation of Medicinal Products
EPAR	European Public Assessment Report
FDA	Food and Drug Administration (U.S.)
HIC	hepatic iron concentration
HPB	Health Protection Branch
HSC	Hospital for Sick Children (Toronto)
IND	Investigational New Drug
LOR	loss of response
MAC	Medical Advisory Committee
MRC	Medical Research Council
MRI	magnetic resonance imaging
MSSA	Medical Scientific Staff Association
NCIC	National Cancer Institute of Canada
NSERC	Natural Sciences and Engineering Research Council
REB	Research Ethics Board
SCD	sickle cell disease
SQUID	superconducting quantum interference device
SSHRC	Social Sciences and Humanities Research Council
TTH	The Toronto Hospital
UTFA	University of Toronto Faculty Association

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Overview

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THIS CASE INVOLVES ISSUES of research ethics and academic freedom so important to the public interest that it has attracted national and international attention. It occurred in a context that quickly developed from the mid-1980s to the mid-1990s of increased pressures on universities, teaching hospitals and individual researchers to seek corporate sponsorship for projects. Public institutions were not conscious of the inadequacy of their policy infrastructures for protecting the public interest in this new environment, and policies and practices had not been changed to take into account the new circumstances.

It was possible for clinical investigators to sign contracts with industrial sponsors for research trials containing provisions that protected the sponsors' interests, but not the public interest or the safety of trial participants. This meant a dispute could arise between the ethical and legal obligations of an investigator to inform participants of unexpected risks, and the contractual right of a sponsor to insist that information on risks not be communicated and to terminate a trial without prior notice. The academic freedom of an investigator to publish adverse findings and inform the scientific community could be at issue.

Such a dispute arose in this case, and it was compounded by oversights, mistakes or misjudgments by individuals, public institutions, a private corporation, and inquiry panels. In some instances the mistakes were understandable, and are more clear with the benefit of hindsight and the full documentation available to us. In other instances, serious wrongs were committed. In these instances substantial redress and calling to account are appropriate.

Clinical research is essential to the health and well-being of Canadians. Industrial sponsors of trials are necessary in many instances, but they must not be allowed to infringe the rights of trial participants, or the rights and obligations of investigators. An important concern is that the policy inadequacies at the heart of this case remain in many institutions across Canada, and unless the lessons are learned and changes made, there will be repetitions.

The L1 research trials & Apotex involvements

Dr. Nancy Olivieri is a specialist in the treatment of hereditary blood diseases. In the early 1990s, she wished to further study an experimental iron-chelation drug, deferiprone (L1), that had shown promise in a pilot study. It appeared to reduce tissue iron loading in a group of transfusion-dependent thalassemia patients at the Hospital for Sick Children (HSC), one of the fully affiliated teaching hospitals of the University of Toronto. The level of funding required for the next stage of testing and development would only be available if she found a corporate sponsor. One of her scientific collaborators, Dr. Gideon Koren, a clinical pharmacologist and then Associate Director for Clinical Research in HSC, negotiated an arrangement with the pharmaceutical manufacturer Apotex Incorporated. Apotex agreed to acquire commercial development rights for L1 and to sponsor clinical trials of the drug. Dr. Olivieri and Dr. Koren signed a contract with Apotex in April 1993 to conduct a new randomized trial to compare L1 with the standard treatment, the drug deferoxamine (DFO). The already existing pilot study was continued with the support of Apotex as a separate long-term trial, although a contract for this trial was not signed with Apotex until October 1995.

It was the hope of the investigators and of Apotex that the trials would lead to the licencing of L1 for therapeutic use and subsequent marketing by Apotex, as an alternative to the onerous DFO treatment. Apotex funding meant the randomized trial was eligible for matching funds from the Medical Research Council (MRC) under its university-industry program. Dr. Olivieri's successful application to MRC, listing an Apotex subsidiary as co-sponsor, was approved by HSC and by the University of Toronto.

The new randomized trial was designed as the pivotal efficacy and safety trial for licencing. Continuation of the non-randomized pilot study that had been ongoing since 1989 was also considered important for assessment of long-term efficacy and safety of the drug. These two studies were the only clinical trials of L1 in any centre that included baseline assessments of liver iron concentration and liver histology, the most accurate measures of the long-term efficacy and safety of an iron-chelation drug. Because inefficacy of chelation would expose patients to chronic iron loading that damages major organs, a significant loss of sustained efficacy would also be a safety issue.

The 1993 contract for the randomized trial contained a confidentiality clause giving Apotex the right to control communication of trial data for one year after termination of the trial. This provision was fully in accordance with existing University of Toronto policy on contract research. There was no confidentiality clause in the 1995 contract for the continued pilot study.

Each of the two contracts specified that Apotex had the right to terminate the corresponding trial at any time. From 1993 until early 1996, the two trials proceeded with ongoing cooperation between the investigators and Apotex.

Trial terminations & legal warnings

In early 1996, Dr. Olivieri identified an unexpected medical risk in data of the patient cohort of the long-term trial: loss of sustained efficacy of the drug. She informed Apotex that she needed to disclose this risk to patients in both trials. Apotex disputed the risk and the need to inform patients, but HSC's Research Ethics Board (REB) accepted that Dr. Olivieri had an obligation to inform patients of the risk she had identified. When Dr. Olivieri moved to inform patients in compliance with a directive from the REB Chair, Apotex terminated both trials abruptly on May 24, 1996. The company simultaneously issued warnings of legal consequences to Dr. Olivieri should she inform patients or anyone else of the risk.

The central issues

At issue was the right of participants in a clinical trial to be informed of a risk that had been identified during the course of the trial by the investigator, and the obligation of the investigator to inform them. Apotex maintained that there was a scientific disagreement, and said that it terminated the trials and issued legal warnings to Dr. Olivieri not to communicate about the risk because it "could not allow such information to be transmitted to patients." However, whether others disagreed or whether the identification would be borne out by other studies was not relevant: when a trial investigator has a reasonable basis to believe she has identified a risk, she must ensure that trial participants are informed about the risk. Otherwise, they are not giving informed consent to continue in the trial. Also at issue was the academic freedom of Dr. Olivieri to publish her findings on L1 and thus inform investigators administering the drug in other centres. Consequently, the public interest was at stake.

Apotex donation discussions

The resulting controversy became linked to a much larger university-industry project. Since the early 1990s the University of Toronto and Apotex had been engaged in discussions for a multimillion-dollar donation, intended to allow a new biomedical research centre to be built that would benefit the University and its affiliated health care institutions. In the spring of 1998, agreement in principle was reached on what then would have been the largest donation the University had ever received. It was to have been matched by other sources to provide the approximately \$92 million needed for the new biomedical research centre. Later in 1998, after the controversy became public, the University and Apotex decided

to suspend discussions until the dispute involving Dr. Olivieri and Apotex was resolved.

Continued administration of the drug

Apotex's termination of the trials without prior notice left patients in an uncertain situation and some did not wish to return to the onerous standard treatment. In early June 1996, the University's Dean of Medicine, Dr. Arnold Aberman, mediated a new arrangement between Dr. Olivieri and Apotex, under the Emergency Drug Release program of Health Canada. Apotex agreed to reinstate the supply of its drug L1 for those patients who appeared to be benefiting. Dr. Olivieri agreed to administer it to those particular patients, on condition they were informed of and accepted the new risk, and agreed to monitoring tests for safety. Such patients were no longer in a research trial and so were not under the jurisdiction of the Hospital's Research Ethics Board. In the fall of 1996, Apotex stopped supplying the drug for the second time, again causing concern to the patients and their parents. Following another intervention by Dean Aberman, Apotex again agreed to reinstate the supply, but the supply of L1 nevertheless remained irregular into early 1997.

Continued associations between Apotex & Dr. Koren

It was agreed during Dean Aberman's June 1996 mediation process that Apotex would continue very substantial research funding to Dr. Koren. According to Apotex, prior to its termination of the L1 trials, Dr. Koren had stated that he agreed with the company's position that there was no risk of loss of sustained efficacy of its drug—contrary to his repeated assurances to Dr. Olivieri that he agreed with her finding of this risk. Unknown to Dr. Olivieri until after the fact, Dr. Koren subsequently re-analysed data from the terminated L1 trials and published findings that the drug was effective and safe. Dr. Koren's publications did not disclose Apotex's financial support for his research, made no reference to the risks of L1 Dr. Olivieri identified, and did not acknowledge her contributions to generating the data he used. The company used Dr. Koren's statements to it and post-trial publications by him in communications with Health Canada to counter Dr. Olivieri's adverse findings on its drug.

Identification of a second risk of L1

In early February 1997, Dr. Olivieri identified a second unexpected risk, potentially more serious than the first, that the drug may cause progression of liver fibrosis. Despite further legal warnings from Apotex, she informed her patients and the regulatory authorities in a prompt way. She counselled patients

to discontinue use of L1 and began making arrangements to transfer them back to the standard treatment, a complex process that takes a number of weeks, since proper administration of DFO requires current test information for each patient. As the newly identified risk was not an acute one, there was time for a safe and orderly transition.

During this transition period, a dispute developed between Dr. Olivieri and Dr. Hugh O’Brodivich, HSC’s Pediatrician-in-Chief. His expertise is not in hematology and, following discussions with Apotex and Dr. Koren, Dr. O’Brodivich appears to have drawn the incorrect conclusion that the newly identified risk was one of acute toxicity. He also incorrectly supposed that the Hospital’s Research Ethics Board (REB) had jurisdiction over the matter and that Dr. Olivieri was obligated to notify the REB of the risk.

The dispute between Dr. Olivieri and Dr. O’Brodivich appeared to have been resolved through discussions and correspondence by early March 1997. At the same time, Apotex began efforts to persuade medical administrators and patients in Toronto, as well as regulatory agencies and the scientific community, that L1 was effective and safe and should be in wider use. Apotex proposed a new treatment arrangement for Toronto thalassemia patients in which annual liver biopsy, the test that had led to the identification of both of the unexpected risks of L1, would not be an integral part of the safety monitoring regime for all patients. Apotex’s proposal was not accepted by Dr. Olivieri who had phased out use of L1 in the clinics she directed. She had the support of hematologist Dr. Michael Baker, Physician-in-Chief of The Toronto Hospital, where adult thalassemia patients received their care under her supervision.

Lack of support for Dr. Olivieri

From May 1996 onward, Apotex repeatedly issued legal warnings to Dr. Olivieri not to communicate on the risks she identified. None of these warnings has been rescinded. Neither HSC nor the University provided effective support to Dr. Olivieri, or took effective action to defend principles of research ethics, clinical ethics and academic freedom. University officials acknowledged that Apotex was acting inappropriately and that the University had a responsibility to defend her academic freedom. However, except for clearly ineffective requests to Apotex to desist made by Dean Aberman in 1996, the University did not take further action to meet this responsibility until early 1999. HSC officials took no effective action to support Dr. Olivieri, until early 1999 when the University and others intervened.

During the first two years of the dispute with Apotex, Dr. Olivieri had legal support through the Canadian Medical Protective Association (CMPA). The very substantial resources CMPA devoted to this case demonstrate both the seriousness

with which Apotex's legal warnings were taken by that physicians' mutual defence organization, and the ineffectiveness of any interventions the University and HSC might have made with Apotex. The primary mandate of CMPA legal counsel was to minimize Dr. Olivieri's legal exposure as an individual client, rather than to protect broad institutional or societal interests. There were instances when Apotex's legal warnings substantially impeded Dr. Olivieri in exercising her academic freedom. Defence of the institutional and societal interests at stake was the responsibility of the University and the Hospital.

In 1997 and 1998 increasing numbers of medical scientists expressed concerns over the lack of effective action by HSC and the University to assist Dr. Olivieri in contending with Apotex's actions. Their representations were not accepted and this led to calls for an independent inquiry into the controversy. In mid-August 1998, more than two years after it began, the controversy became public. During the 1997–1998 period, the HSC scientists who became Dr. Olivieri's principal supporters, Drs. Helen Chan, John Dick, Peter Durie and Brenda Gallie, began their involvement.

Apotex's licencing applications

Apotex submitted licencing applications for L1 in several jurisdictions in early 1998. In these applications, Apotex now alleged that the data from the terminated Toronto trials had been compromised by protocol violations by Dr. Olivieri. Conduct of a short-term safety trial had been one of the licencing requirements set out by the Federal Drug Administration (USA), and such a trial had been designed and organized for Apotex at sites outside Canada by Dr. Olivieri on a consulting contract. The company now maintained that this short-term trial, whose primary objective was an assessment of known acute-toxicity effects of L1, was the pivotal efficacy and safety trial for licencing purposes. Unlike the randomized and long-term trials in Toronto, the protocol for the short-term safety trial did not include baseline and annual determination of liver iron concentration and liver histology for all participants.

Criticism of Dr. Olivieri

Shortly after the L1 controversy became public, without first giving Dr. Olivieri an opportunity to respond, the HSC Executive issued a public statement repeating allegations made privately to it by Apotex against the quality of her scientific work. A week later, the Hospital unilaterally established a review of the controversy and appointed Dr. Arnold Naimark of the University of Manitoba as the Reviewer. The choice of Reviewer and structure of the Review became subjects of controversy and when efforts to resolve this controversy were unsuccessful, Dr. Olivieri and her supporters declined to participate in that Review.

During the Naimark Review, Dr. Koren and Dr. O'Brodovich put forward incorrect testimony against Dr. Olivieri on several topics. Dr. Aileen Moore, who became Chair of the HSC Research Ethics Board shortly after the Toronto trials were terminated, put forward incorrect testimony that a research trial of L1 continued after both trials had in fact been terminated. The Naimark Review accepted the testimony of these witnesses as true, and said that the patients on L1 were still in a research trial and that Dr. Olivieri had failed in the obligation to report the second risk she identified to the REB. These findings were incorrect: when that risk was identified, the patients were not in a research trial and she did not have that reporting obligation. In fact, the documentation shows Dr. Olivieri fulfilled all the reporting obligations she actually had, and put the patients' right to be informed ahead of concerns of possible legal action against her by Apotex.

During this period of the Naimark Review, Dr. Koren began sending anonymous letters to the media and to colleagues disparaging Dr. Olivieri and Drs. Durie, Gallie and Chan.

Disputes over resources for the sickle cell disease program

Because of demographic changes in the Toronto region, the number of patients with thalassemia and sickle cell disease (SCD) treated in the HSC hemoglobinopathy clinic directed by Dr. Olivieri grew substantially. This came at a time of erosion in health care funding by governments that caused resource problems in hospitals across Canada. In the mid-1990s the HSC administration selected the SCD program as one of several to be decentralized to regional hospitals, as part of a new regional pediatric care network. Dr. Olivieri opposed this move, citing evidence from outcomes in major American centres that patients with this disease are best cared for in tertiary hospitals by experienced specialists. Disagreements between her and HSC administrators over the proposed decentralization and other resource issues escalated in the spring of 1996. The correspondence shows that by the time Apotex terminated the L1 trials in May 1996, some HSC administrators viewed Dr. Olivieri as a demanding and challenging subordinate, while she viewed some of them as unreasonable and undeserving of deference.

The task of HSC administrators in realizing this decentralization objective was later complicated by opposition from SCD patient support groups, and by the view of administrators in The Toronto Hospital (where adult SCD patients received their care) that decentralizing SCD patient care might not be the best approach. Periodic flare-ups in the disputes over resources came to a head at the beginning of 1999, when HSC summarily removed Dr. Olivieri from her post as director of its hemoglobinopathy program, with no opportunity to respond to HSC charges against her.

Interventions by the University & others

On January 6, 1999, the same day HSC removed Dr. Olivieri from the directorship, it issued directives that Dr. Olivieri and Drs. Chan, Durie and Gallie were not to discuss their concerns publicly. As a result of these two HSC actions, legal counsel for Dr. Olivieri, distinguished scientists from abroad, the Canadian Association of University Teachers, the University of Toronto Faculty Association, and the University of Toronto administration intervened. University President Robert Prichard mediated an agreement that was signed on January 25, 1999 by HSC and Dr. Olivieri to resolve a range of issues. The agreement restored Dr. Olivieri's authority over research and clinical care of hemoglobinopathy patients in HSC, and affirmed the right to academic freedom for University faculty working at HSC. It also provided an assurance of HSC financial support for Dr. Olivieri in the event of legal action against her by Apotex. This was the first time HSC accepted responsibility to provide effective support to Dr. Olivieri, who since May 1996 had been subject to legal warnings by the company.

Despite this signed agreement, problems continued to arise between HSC and Dr. Olivieri. Dean Aberman, Dr. Baker and, later in 1999, President Prichard and Dr. David Naylor, the new Dean of Medicine, again became involved in mediative processes. These efforts have not yet been successful in resolving outstanding issues.

Further criticism of Dr. Olivieri

Upon receipt of the Naimark Report in December 1998, HSC's Board of Trustees declared (incorrectly) that Dr. Olivieri had "failed" in a reporting obligation, namely, to notify the REB of an unexpected risk in a timely way. The Board directed the Hospital's Medical Advisory Committee (MAC) to inquire into her conduct. During this inquiry, Dr. Koren and Dr. O'Brodovich introduced new allegations concerning Dr. Olivieri's care of thalassemia patients during the period in early 1997, when the second risk of L1 was identified and patients were being transferred to standard therapy. They alleged that a test Dr. Olivieri had performed on some patients, liver biopsy, was a risky procedure and was not clinically indicated. These allegations were based on incorrect information that could easily have been corrected if anyone on the MAC had checked the medical literature or well-established practice in the Hospital. In fact, Dr. O'Brodovich had been repeatedly advised in writing by Dr. Olivieri that these biopsies were being scheduled, and of the clinical indication for them, and he had not opposed them at the time.

Without disclosing the allegations and testimony of its witnesses to Dr. Olivieri, the MAC believed them, even though they were made by persons who did not have relevant medical expertise, no member of the MAC had the relevant expertise, and the MAC did not consult independent experts. Because she did not know the case against her, Dr. Olivieri was deprived of a fair opportunity to respond. The MAC issued a report based on the undisclosed information. It was not until after this, and legal representations on her behalf, that some of the allegations and testimony were disclosed to her.

In a press conference on April 27, 2000, the Hospital's Board and MAC announced they were referring the allegations against Dr. Olivieri, cast in the form of publicly enumerated concerns, to the College of Physicians and Surgeons of Ontario (CPSO) and to the University of Toronto for investigation.

Disciplinary action against Dr. Koren

The Hospital took its public action against Dr. Olivieri two weeks *after* the Presidents of the Hospital and the University had disciplined Dr. Koren for gross misconduct, namely, sending anonymous letters disparaging the personal and professional integrity of Dr. Olivieri and Drs. Chan, Durie and Gallie, and

persistently lying to conceal his actions. Dr. Olivieri *et al.* had lodged a complaint against Dr. Koren in May 1999 on the basis of substantial forensic evidence identifying him as author of the letters. He denied responsibility and lied for many months to frustrate and obstruct the Hospital's investigator, admitting responsibility only after Dr. Olivieri *et al.* obtained additional evidence (DNA) identifying him as the author. Dr. Koren was provided with full particulars of the case against him and a fair opportunity to respond, before the disciplinary action was imposed on April 11, 2000.

This dishonest conduct by Dr. Koren was ample reason to doubt, and to re-examine carefully, the information he and persons associated with him had brought forward to the Naimark and MAC inquiries, before taking such serious action against Dr. Olivieri in such a public manner. This apparently was not done by the MAC or the Board. If they had done so, they would have seen that Dr. Koren's allegations and testimony were contradicted not only by documents available to him, but by earlier correspondence written by him.

Allegations by Apotex

The two unexpected risks of L1 had been identified by Dr. Olivieri in data derived from liver biopsy specimens. Apotex subsequently claimed that liver biopsy was needless, risky and not generally accepted as a diagnostic guide to treatment for transfusion-dependent thalassemia patients. This claim is contradicted by the medical literature where it is clear that liver biopsy is extremely low risk, and is needed to guide appropriate dosage of medication for these patients and to assess possible adverse effects of treatment. The allegations and testimony by Dr. Koren and Dr. O'Brodovich to the MAC that liver biopsy was unnecessary and risky, and done by Dr. Olivieri only for research, came after the similar criticisms of this procedure by Apotex.

Apotex used the incorrect findings against Dr. Olivieri in the Naimark Report, and the public referral of the MAC allegations to the CPSO and the University, to defend the reputation of its drug L1 in legal proceedings.

Continued Apotex donation discussions

In 1999 the University of Toronto and Apotex had further discussions on the multi-million dollar donation which they had been discussing since the early 1990s and on which they had reached agreement in principle in 1998. Apotex requested assistance from University President Prichard in lobbying the Government of Canada against proposed changes to drug patent regulations that would adversely affect the company's revenues. President

Prichard wrote to the Prime Minister, stating that the proposed government action could jeopardize the building of the University's proposed new medical sciences centre. The President subsequently apologized to the University community, saying he had acted inappropriately. The lobbying efforts were unsuccessful, and later in 1999 Apotex withdrew from the 1998 agreement in principle on the donation. In 2000 it was announced that Apotex had made a smaller multi-million dollar donation to the University.

Ongoing controversy

Five years after Apotex terminated the Toronto trials and issued its first legal warnings to Dr. Olivieri, the controversy continues, widened and intensified. Several proceedings were initiated. Drs. Olivieri, Chan, Dick, Durie and Gallie lodged grievances against the University administration. HSC administrators initiated court action to quash summonses for documents issued by the University grievance panel. Dr. Olivieri initiated a libel suit against Apotex over public statements made by company officers. The company responded with a countersuit. Dr. Olivieri requested a judicial review in a European court through which she is contesting the validity of a restricted marketing licence for L1 granted to Apotex in 1999, on the basis of her claim that Apotex misrepresented data on the drug and incorrectly alleged that she had committed serious protocol violations.

The report of this Inquiry

A substantial amount of incorrect information on this case has been put into the public domain, and the central issues have often been obscured. Previous reviews were compromised by one-sided, sometimes incomplete, sometimes incorrect, and sometimes false information put forward to them. Perhaps not surprisingly, they arrived at incorrect conclusions regarding Dr. Olivieri's conduct. The Naimark Review had not been alerted to the possibility of misleading testimony by Dr. Koren's dishonest conduct being known, and neither it nor the MAC pursued inconsistencies and contradictions in the information before them.

The present Inquiry had several advantages over previous reviews. During the two years of our Inquiry, important documents became available that were not considered by the previous reviews. This is because the very extensive documentation available to us included for the first time not only the documentation of individuals and institutions participating in the Naimark Review, but also documentation of Dr. Olivieri and her supporters. We have had the advantage also of being able to take the time necessary to do the detailed analysis of the hundreds of primary documents we had available. As a result, we believe we have for the first time a complete picture of actions and events and have been able to arrive at an accurate understanding of this complex case. Our lengthy and detailed report relies principally on the documents we examined, and it lays out clearly the basis of our findings and conclusions, so that interested persons can follow our analysis. The facts of the case deserve to be known widely, in order that important lessons can be learned.

Our findings and recommendations follow, but in essence:

- **Apotex** should not have attempted to impede Dr. Olivieri from informing patients, regulators and the scientific community of the risks of the drug L1 she identified. This was against the public interest and was inappropriate conduct by the company.
- **The Hospital for Sick Children and the University of Toronto** could and should have effectively supported Dr. Olivieri in the exercise of her rights and obligations, as this was a matter of academic freedom and protection of the public interest, but they did not do so.
- **The Hospital for Sick Children** denied due process to Dr. Olivieri in several important matters, including the Medical Advisory Committee (MAC) proceedings.
- **Dr. Koren's** conduct as a witness in the Naimark Review and the MAC proceedings, and his conduct as author of certain publications on L1, was

unacceptable. He should be called to account by the Hospital for Sick Children and the University of Toronto.

- **The adverse findings** against Dr. Olivieri by the Naimark Review and the MAC allegations against her are incorrect.
- **The Hospital for Sick Children** should withdraw its referrals of allegations to the College of Physicians and Surgeons of Ontario and the University of Toronto.
- **Dr. Olivieri** should be given redress for the unfair treatment she has received.
- **The general features** of this situation are not unique to the Hospital for Sick Children and the University of Toronto, and given the current absence of the necessary protections, it could occur at many institutions across Canada. As we specify in our sections on recommendations and lessons to be learned, it is essential to put in place measures to ensure that, in the conduct of clinical research trials, the public interest is protected from inappropriate actions by trial sponsors.

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Lessons to be Learned

FOR EVERYONE: There are important lessons to be drawn from this story. In a Canada-wide context of increasing reliance on corporate sponsorship, where the largest proportion of research funding for medical research and clinical trials is now provided by private companies, this dispute holds important lessons for investigators, university faculties, Research Ethics Boards, administrators of hospitals and universities, the Canadian Association of University Teachers (CAUT), the Association of Universities and Colleges of Canada (AUCC), research granting councils, industrial firms and regulatory agencies. Unless the lessons are learned, everyone will lose—the public, the researchers, the hospitals, the universities and the private companies, as they have in this case. It is important to recognize that the circumstances that gave rise to this case are not isolated—they illustrate a system-wide problem.

The pharmaceutical industry is very powerful, and has substantial resources to promote its interests. Unless governments, granting councils, universities, hospitals, research ethics boards and researchers work in concert to protect the independence of investigators with nation-wide, well-publicized and effectively implemented regulatory mechanisms, the public interest is likely to suffer.

A principle of the highest priority is at stake: namely, that the safety of research subjects in clinical trials and the integrity of the research process are more important than corporate interests. In an era of increasing reliance on corporate funding of research, university and hospital administrations need to be doubly vigilant in protecting this principle. If university/hospital-industry partnerships are to bring benefits (other than to the partners), then there must be clear rules governing the relationships, rules that protect the right of researchers to communicate (including publication) findings of risk that may displease the sponsor.

FOR INVESTIGATORS: Clinical researchers should never sign contracts, protocols or agreements that allow sponsors to restrict communication (including publication) about risks they identify.

FOR RESEARCH ETHICS BOARDS: Research ethics boards should be vigilant against restrictions on communication in the wording not only of protocols but also of contracts and investigator agreements. In addition to reviewing protocols, they should review the wording of associated contracts and agreements, and should not give approval for the study if any of these documents contain wording that would restrict the investigators in communication (including publication) about risks they identify.

FOR INDUSTRY: Companies should not attempt to suppress or control results. This is in their long-term interest as the revelation of such actions will damage their reputation with the public, and with regulatory agencies. Any firm with a reputation for such suppression or control is unlikely to be viewed as a desirable sponsor of research by the best researchers or outstanding universities, or trusted by prescribing physicians, potential research participants and potential customers for the drugs they market.

FOR UNIVERSITIES: All universities should have a policy prohibiting clauses in contracts, investigator agreements or protocols restricting communication (including publication) of risks identified in research projects, particularly clinical trials. They should have procedures in place to ensure this policy is followed in practice. It is their duty to act strongly in support of their researchers if the researchers' independence or academic freedom is threatened by any sponsor. If they fail in this duty, the public interest and public safety are in jeopardy.

FOR HOSPITALS: All research hospitals should have in place a policy, and measures to ensure implementation, that prohibits agreements, contracts or protocols that have clauses that restrict communication (including publication) of risks identified in research projects, particularly clinical trials. They should act strongly in support of their clinical researchers if the researchers' independence or academic freedom is threatened by any sponsor, in order to fulfil their responsibility to protect the safety of their patients, whether or not the patients are enrolled in a research trial.

FOR UNIVERSITIES & HOSPITALS: Universities and their affiliated hospitals should strongly support the independence, authority and ability of their research ethics boards to help them ensure all research involving human subjects being conducted in their institutions meets ethical standards.

All universities, and all hospitals affiliated with universities, should have policies on development to ensure that fund-raising possibilities do not have an adverse impact upon the institution's willingness or ability to protect and promote academic freedom and the public interest. If senior administrators are involved in discussions on major donations, it may be difficult for them to maintain their objectivity when a potential donor becomes engaged in a dispute with a researcher. Effects of donations on institutions may be pervasive and subtle due to a natural wish to oblige donors, and it is important to discuss such influences openly.

Universities and their affiliated hospitals should put in place grievance and arbitration procedures for all persons holding academic appointments (including clinical researchers, bioethicists and biomedical scientists) who work in the hospitals, that encompass all important employment matters, including academic freedom, appointments and hospital privileges.

FOR GRANTING COUNCILS: All research granting councils should have a policy prohibiting clauses in contracts, investigator agreements or protocols, that could be used to restrict communication (including publication) of risks to human health identified in research projects, particularly clinical trials. The councils should make compliance with such policies and procedures a requirement for all research carried out in any institution to which they award funds, and the councils should actively monitor compliance. If this is done, it will not be possible for industrial sponsors to move funding to institutions that allow them to control disclosure of results. If this is not done and other institutions are known to be more lenient and available, pharmaceutical manufacturers could stop carrying out projects at institutions that ask for stringent patient protections and unrestricted disclosure of risks. A united stance would avoid any likelihood of a race to the bottom—such a race would be to the detriment of the public interest.

FOR THE ASSOCIATION OF UNIVERSITIES AND COLLEGES OF CANADA & THE CANADIAN ASSOCIATION OF UNIVERSITY TEACHERS: Both the AUCC and the CAUT should develop policies and procedures appropriate to the current environment of health research, in their own spheres, and they should cooperate in efforts to ensure that individuals, institutions, corporations and agencies of governments learn the lessons outlined in this report.

20 Report of the Committee of Inquiry on the Case Involving Dr. Nancy Olivieri, the Hospital for Sick Children, the University of Toronto, and Apotex Inc.

FOR REGULATORS: If it is to maintain the public trust and safeguard the public interest, the federal regulatory agency should act in a way that strictly upholds the *Food and Drugs Act* and *Regulations* and should exercise its authority in the public interest. Health Canada should always put the public interest in safety above private corporate interests, and should review and where necessary revise legislation, regulations or policy to ensure this.

FOR FEDERAL & PROVINCIAL GOVERNMENTS: Because safeguards for independence of investigators are usually less robust in non-university settings, it is important that there be oversight of the conduct of clinical trials run outside university teaching hospitals. There has been a significant increase in the number of such trials in North America. The *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans* is a valuable guide on many aspects, but it does not apply to research conducted in institutions or organizations which receive no funding from the three Canadian research granting councils (CIHR, SSHRC, NSERC). More broadly still, federal and provincial governments should work together to develop a way to regulate the conduct of research involving human subjects. They should consider and report back to the Canadian public on the option of legislating to govern the ethical conduct of *all* research involving human subjects conducted in Canada. In addition, the federal government should ensure that Health Canada has the human and financial resources, and the legislative powers, necessary to protect the public interest in the regulation (review, approval, and monitoring) of pharmaceuticals in Canada.

C

Findings

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Contextual

1 | The Hospital for Sick Children (HSC) did not have an adequate policy infrastructure to protect patients and the public interest in the conduct of clinical trials, and this was a contributing factor in the development of the controversy.

2 | The University of Toronto Publication Policy in regard to contract research allowed industrial sponsors to impose confidentiality restrictions for one year following the termination of a project. This applied to sponsored research generally, including sponsored clinical trials. After the L1 dispute became public in 1998, the University stated that its policy would not have allowed such restrictions. This was not true. In 2001 the University announced that it and its affiliated health care institutions were changing their policies so as to disallow confidentiality clauses in research contracts that could be used to deter clinical investigators from disclosing risks to patients and others. By the act of announcing this important and necessary change, the University acknowledged that its prior policy was inappropriate for clinical research.

3 | The University of Toronto and Apotex had been engaged in discussions on a major donation since 1991. They reached agreement in principle on a multi-million dollar donation in the spring of 1998 (\$20,000,000 to the University and \$10,000,000 to the University for affiliated teaching hospitals). In the fall of 1998, after the L1 controversy received widespread media coverage, the University and Apotex agreed to suspend donation discussions until the matters in that dispute were “resolved” and Apotex “cleared of wrongdoing.” In 1999, while the L1 controversy continued, discussions on the major donation between the University and Apotex resumed. At the request of Apotex, the President of the University of Toronto wrote to the Prime Minister of Canada to delay action on proposed changes to drug patent regulations that could adversely affect Apotex’s business. The President later apologized for his letter. After the Federal Government proceeded with the changes, Apotex withdrew from the agreement in principle. In a list of donors published by the University in late 2000, Apotex was shown as having made a smaller donation to the University, between \$5,000,000 and \$9,999,999.

4 | The Medical Research Council (MRC), through its university-industry program, encouraged clinical researchers to seek industrial sponsors, but did not put in place adequate guidelines to ensure the safety of trial participants and disclosure of risks. For instance, MRC did not prohibit inappropriate confi-

dentiality clauses in contracts between investigators and industrial co-sponsors. Also, an industrial sponsor could unilaterally terminate a trial co-sponsored by MRC, without any MRC requirement being in place to ensure that patients were not adversely affected by the premature termination.

5 | HSC had no effective grievance procedure for its medical and scientific staff, and it has not yet put such a procedure in place.

Chronological

6 | After the drug L1 showed promise in an MRC-funded pilot study, Dr. Nancy Olivieri applied to MRC for a larger grant to conduct a randomized trial to compare the efficacy and safety of L1 with the standard iron-chelation therapy, deferoxamine (DFO). This application was not successful, but she was invited to re-apply in light of written comments of the reviewers. These included the suggestion that she apply under MRC's university-industry program.

7 | Dr. Gideon Koren, a co-investigator with Dr. Olivieri on the pilot study and Associate Director for Clinical Research in the HSC Research Institute, approached the pharmaceutical manufacturer Apotex Inc. through his long-time colleague in the University and in HSC, Dr. Michael Spino. Dr. Spino had recently joined Apotex as a full-time employee, while still retaining his status as a professor of pharmacy in the University and his laboratory facilities in HSC. Apotex agreed to acquire the commercial development rights for L1 and to sponsor clinical trials.

8 | Dr. Koren and Dr. Olivieri signed a contract in 1993 with Apotex Inc. for the randomized trial (LA-01). This contract contained a one-year, post-termination confidentiality clause. This was in accordance with existing University and Hospital policy. Nevertheless, Dr. Koren and Dr. Olivieri should have been more alert to the implications of this clause in the contract and should have refused to sign it without appropriate modifications.

9 | Apotex funding enabled Dr. Olivieri to re-apply to MRC under its university-industry program for co-sponsorship of the randomized trial. This application was successful.

10 | Apotex also agreed in 1993 to supply L1 free of charge for continuation of the pilot study as a long-term efficacy and safety trial (LA-03), but there was no formal contract for this trial until 1995.

11 | The Research Ethics Board (REB) of HSC approved protocols for both the Toronto L1 trials (LA-01 and LA-03) without reviewing the associated contracts to ensure that the contracts did not breach ethical standards or norms. The confidentiality clause in the LA-01 contract had an inappropriate confidentiality clause—it specified that Apotex had the right to suppress information during the trial and for one year after its termination. The REB also did not require inclusion of provisions in the protocol to protect the interests of trial participants in the event of premature termination by the industrial sponsor.

12 | Dr. Olivieri signed a consulting contract with Apotex in June 1995 for work on a short-term safety trial of L1 at international sites (LA-02), that the Federal Drug Administration (USA) had specified as a licencing requirement. This had a three-year, post-termination confidentiality clause that was not in compliance with University of Toronto policy. Dr. Olivieri had no patients enrolled in this trial, she was not an “investigator,” and this contract (including its confidentiality clause) was not relevant to the two Toronto trials (LA-01 and LA-03). However, it was nevertheless inappropriate for her (or any clinical investigator) to sign a contract containing such a clause.

13 | Confidentiality clauses of the type then allowed are not appropriate for clinical trials. They can be used by an industrial sponsor to suppress information it considers adverse to its commercial interests, including information concerning risks to trial participants, or to patients in a post-trial treatment arrangement. As invoked in this case by Apotex, such confidentiality clauses offend public policy.

14 | Dr. Koren and Dr. Olivieri signed a contract in October 1995 with Apotex Inc. for continuation of the pilot study as long-term efficacy and safety trial (LA-03). This contract had *no* confidentiality clause. The two unexpected risks of the drug L1 were identified by Dr. Olivieri in data of this trial.

15 | Apotex had the right under the LA-01 contract to terminate the LA-01 trial and it had the right under the LA-03 contract to terminate the LA-03 trial.

16 | In 1996 Dr. Olivieri identified an unexpected risk of L1—loss of sustained efficacy—in data of the LA-03 trial. She believed she was obligated to inform trial participants and the Research Ethics Board (REB), and she prepared a report on the risk for the REB. Apotex disputed this finding and opposed informing patients. On reviewing Dr. Olivieri’s report, the REB Chair Dr. Zlotkin agreed that trial participants should be informed and accordingly directed her to revise the information and consent forms for participants.

17 | Dr. Olivieri submitted the revised information and consent forms to the REB on May 20, 1996 and sent a copy to Apotex. On May 24, 1996 Apotex exercised its rights under the LA-01 and LA-03 contracts and terminated *both* trials.

18 | Apotex notified the Canadian regulatory agency, the Health Protection Branch (HPB) of Health Canada that it had terminated both Toronto trials, LA-01 *and* LA-03, on May 24, 1996.

19 | Dr. Olivieri notified the Hospital's Research Ethics Board (REB) in writing that both Toronto trials, LA-01 *and* LA-03, had been terminated by Apotex on May 24, 1996.

20 | Apotex showed disregard for the interests and concerns of patients when, without prior notice, it terminated both trials and stopped supplying its drug L1 in May 1996.

21 | Apotex terminated both Toronto trials (LA-01 and LA-03) in an attempt to prevent Dr. Olivieri from informing patients and others of a risk of L1 she identified, and it issued warnings of legal action against her should she inform patients or anyone of the risk without its prior written consent. Apotex has never consented to any disclosure by Dr. Olivieri of risks she identified.

22 | Apotex had no contractual basis for legal warnings in regard to LA-03 data, but this important fact does not seem to have been appreciated and did not play a role in the developing controversy.

23 | Against the wishes of Dr. Olivieri, and against the recommendation of its own Expert Advisory Panel, Apotex refused to reinstate either the LA-01 or the LA-03 trial. The Expert Advisory Panel urged that the trials be reinstated so that it could be clarified whether some patients benefited and what factors determined potential benefit. Only by continuing the trials could participants and thalassemia patients elsewhere have the benefit of knowing whether L1 was sufficiently effective and safe to be licenced as therapy for some patients.

24 | When Apotex terminated the trials without notice, Dr. Arnold Aberman, the University's Dean of Medicine, mediated a new arrangement under which those patients who wished to continue on L1, and in whom it appeared to be working, could do so, as patients of Dr. Olivieri and being monitored by her. This new treatment arrangement was under Health Canada's Emergency Drug Release (EDR) program and was not a research trial. The REB had no jurisdiction over this clinical arrangement.

25 | Those patients who wished to continue on L1, and for whom it was considered sufficiently safe and beneficial in their individual cases, were permitted to continue, provided they were informed of and accepted the new risk, and agreed to safety monitoring tests. Under EDR, Dr. Olivieri was required to monitor patients and report the results to Apotex and Health Canada.

26 | Apotex showed disregard for the interests and concerns of patients when it stopped supplying its drug a second time, in October 1996. Dean Aberman intervened again in an effort to have the supply reinstated, but the supply remained irregular into early 1997.

27 | The situation in regard to research fellows who had been engaged for fixed periods to work on the trials was left uncertain when Apotex terminated the trials without notice. It was agreed during Dean Aberman's mediation process that the fellows would continue to be employed for their contracted periods, under continuing supervision of Drs. Koren and Olivieri during the close-out of the terminated trials. Thereafter they would work under Dr. Koren's supervision on his research projects. Apotex provided additional funds for salary support for the research fellows during the post-trial period. Contrary to practice by other members in his Division in the University's Department of Pediatrics, Dr. Koren did not disclose that Apotex was the source of a \$250,000 research grant he received that year, that was listed in his University department's annual grant listing. Nor did he disclose the subject matter of the research this grant funded.

28 | Before and after Apotex terminated the Toronto trials in May 1996, Dr. Koren gave assurances to Dr. Olivieri that he agreed with her finding of a risk of L1 and her view that trial participants needed to be informed of it. Apotex stated that during the same period, Dr. Koren gave assurances to the company that he agreed with its contrary position on these matters.

29 | Dr. Koren was senior author of two abstracts based on analysis of data from the two terminated trials. These were presented at a conference in Malta in April 1997 by their first author, Apotex employee Dr. Tricta, who had not been involved in the work of either trial. They reported that L1 was effective and safe in the treatment of thalassemia patients. This was inconsistent with the findings Dr. Olivieri had published in two abstracts based on data from the same trials in December 1996. Dr. Koren's Apotex-funded research fellows were included among his co-authors on his abstracts for the Malta conference. The abstracts did not disclose the Apotex funding support for Dr. Koren or the fellows, did not acknowledge Dr. Olivieri's contributions to generating the

data, and did not note that she had already published abstracts based on this data.

30 | In communications with Health Canada in 1996 and 1997, to counter Dr. Olivieri's adverse findings on L1, Apotex used Dr. Koren's assurances that he supported its position on the drug, as well as publications by him supporting the company's position on the efficacy and safety of the drug.

31 | In early 1997, Dr. Olivieri identified a second unexpected risk of L1, when she and liver pathologist Dr. Ross Cameron conducted a historical review of charts of patients who had been in the long-term trial (LA-03). She informed in a prompt way all those she was obligated to inform: the patients, Apotex and Health Canada. She also promptly informed Dr. Koren. She initiated steps to inform the scientific community so that physicians prescribing L1 in other centres would learn of the newly identified risk.

32 | Apotex issued more legal warnings to deter Dr. Olivieri from communicating this second unexpected risk of L1 to anyone. However, she was legally and ethically obligated to communicate the risk to those taking, or prescribing the drug as there were potential safety implications for patients, and she fulfilled these obligations despite the legal warnings.

33 | Some of Apotex’s 1997 legal warnings to Dr. Olivieri were to deter her from presenting her findings on the two unexpected risks of L1 at the same April 1997 conference in Malta at which Dr. Koren’s abstracts were being presented. On CMPA legal advice, she initially withdrew her already submitted abstract, but upon learning that Dr. Koren was presenting abstracts with an Apotex employee, she re-submitted and presented her abstract, notwithstanding the legal warnings from Apotex.

34 | Apotex acted against the public interest in issuing legal warnings to Dr. Olivieri to deter her from communicating about risks of L1. None of the legal warnings has been rescinded.

35 | Apotex’s legal warnings violated Dr. Olivieri’s academic freedom.

36 | The representative of Apotex most prominent in the repeated and continuing legal warnings violating Dr. Olivieri’s academic freedom was its Vice-President, Dr. Michael Spino, who continues to hold the status of a professor in the University’s Faculty of Pharmacy. We have seen no evidence that his conduct in violating this fundamental freedom has been effectively addressed by the University.

37 | The Hospital for Sick Children and the University of Toronto did not provide effective support either for Dr. Olivieri and her rights, or for the principles of research and clinical ethics, and of academic freedom, during the first two and a half years of this controversy. After the controversy became public in 1998, the University stated publicly that it had provided effective support for Dr. Olivieri’s academic freedom, but this was not true.

38 | Notwithstanding Apotex’s legal warnings and the lack of support from the University and the Hospital, Dr. Olivieri complied with all of her ethical obligations, including reporting obligations, and she published her findings. During the period summer 1996–summer 1998, the only effective support she had in exercising her rights and responsibilities in the face of the Apotex legal warnings was from the Canadian Medical Protective Association (CMPA), although it was not always effective. In keeping with their mandate, the advice of legal counsel provided by CMPA was largely aimed at minimizing Dr. Olivieri’s legal exposure, not at protecting societal or institutional interests.

The University and the Hospital should have ensured defence, including legal defence, of these broader interests.

39 | The very substantial resources CMPA devoted to this case demonstrate the seriousness with which CMPA, and the lawyers CMPA engaged to represent her, viewed the Apotex legal warnings, and demonstrate the ineffectiveness of any support the Hospital and the University gave.

40 | HSC Pediatrician-in-Chief Dr. O’Brodivich put forward incorrect allegations and testimony, in addition to seriously incomplete testimony, against Dr. Olivieri to the Naimark Review and to the Medical Advisory Committee. In this he used information from Dr. Koren and cooperated with Dr. Koren. Dr. O’Brodivich was seriously neglectful in not checking the validity, or ensuring the completeness, of his testimony.

41 | Dr. Koren attempted to discredit Dr. Olivieri by dishonest means:

- He was the author of anonymous letters to the press and others against Dr. Olivieri and her supporters, for which he denied responsibility for many months.
- He put forward false allegations and testimony against Dr. Olivieri to the Naimark Review, and to the MAC inquiry that followed.

42 | In addition to false allegations and testimony, Dr. Koren put forward incorrect allegations and testimony against Dr. Olivieri to the Naimark Review and to the MAC inquiry that he should have known were incorrect, because they were contradicted in documents available to him. He was seriously neglectful in putting these forward.

43 | Dr. Koren lied persistently for many months about his responsibility for the anonymous letters, and did not admit responsibility until after he had been identified by DNA evidence.

44 | The University and the Hospital disciplined Dr. Koren on April 11, 2000 for the misconduct to which he admitted: his series of anonymous letters disparaging Dr. Olivieri and several colleagues; and lying persistently about responsibility for the letters.

45 | After Dr. Koren admitted to writing and sending anonymous letters against Dr. Olivieri and her supporters, Dr. O’Brodivich, the Medical Advisory Committee (MAC) and the HSC Board of Trustees had a responsibility to review and assess carefully all the allegations and testimony Dr. Koren had put forward both to the Naimark and MAC reviews, and all allegations and testimony by other witnesses which relied in any way upon

information given to them by Dr. Koren. We have no evidence that they fulfilled this responsibility.

46 | Neither the University nor the Hospital has properly addressed the conduct of Dr. Koren in putting forward false allegations and testimony against Dr. Olivieri to the Naimark Review and to the MAC, or taken any action to correct the resulting situation.

47 | Research Ethics Board (REB) Chair Dr. Aideen Moore put forward seriously incorrect testimony in regard to the period after Apotex terminated both Toronto trials of L1. Namely, she said that the long-term trial of L1 (LA-03) continued, and continued under REB jurisdiction, after May 1996 when both trials had in fact been terminated and never reinstated. She put forward this testimony despite the fact that the correct information was available to her as REB Chair in documentary form in the files of the REB. Her incorrect testimony was relied on by Dr. O’Brodivich, the Naimark Review and the MAC. It was also cited by Dr. Koren to bolster his allegations and testimony against Dr. Olivieri, despite the documented fact that he himself knew Dr. Moore was wrong. Dr. Moore was seriously neglectful in not checking REB records wherein it was documented that both trials had been terminated on May 24, 1996.

48 | The Naimark Review and the MAC inquiry apparently were not provided with some important, relevant information by persons they interviewed. For instance, the formal notice to the REB by Dr. Olivieri and her HSC Division Chief Dr. Freedman that the long-term trial (LA-03) had been terminated, a notice that had been received by the REB on August 1, 1996, and a centrally important document, was not cited in the reports of either the Naimark Review or the MAC and must be assumed not available to them.

49 | The adverse findings against Dr. Olivieri in the reports of the Naimark Review and HSC’s Medical Advisory Committee are incorrect and based on incomplete, incorrect and false testimony.

50 | The misconduct by Dr. Koren in putting forward false and seriously neglectful testimony against Dr. Olivieri to the Naimark Review and the Medical Advisory Committee, and the uncritical acceptance of his testimony, are significant factors in the L1 controversy being prolonged and widened.

51 | Dr. Koren violated accepted standards of conduct in regard to publication in biomedical journals, when he published an article in *Therapeutic Drug Monitoring* in 1999 on Apotex’s drug L1 without disclosing the company’s financial support for his research, without acknowledging the contributions of Dr. Olivieri and others to generating the data he used or giving them an

opportunity to review or participate in the publication, and without noting previous publications on risks of the drug. We have seen no evidence that either the University or the Hospital has yet taken appropriate action to address this improper conduct.

52 | The Hospital for Sick Children took actions that were harmful to Dr. Olivieri's interests and professional reputation, and disrupted her work. In each instance, the adverse actions were taken without providing due process. She was provided neither with the case she was expected to meet, nor a fair opportunity to respond, prior to the actions being taken. These included:

- wide dissemination on September 1, 1998, of unsupported allegations made privately to the HSC Executive by Apotex against the quality of her work;
- removal from her program directorship on January 6, 1999;
- completion by a subcommittee of the Medical Advisory Committee (MAC) in January 2000 of a report based on allegations and testimony that had not been disclosed to Dr. Olivieri, and endorsement of that report by the MAC; and
- public referral of allegations made by the MAC to external bodies on April 27, 2000.

The matter of the program directorship was resolved through the intervention of the University and other parties, but the other matters remain outstanding.

53 | The action taken by the HSC Board of Trustees and the MAC on April 27, 2000 to publicly refer the MAC allegations, cast in the form of enumerated "concerns," to the College of Physicians and Surgeons (CPSO) and to the University's Faculty of Medicine represented an abdication of responsibility and an abuse of process. The MAC investigation into Dr. Olivieri's conduct was directed by the Board on the basis of incorrect findings in the Naimark Report. The Board's directive did not instruct the MAC to provide due process, and due process was not provided to Dr. Olivieri. The MAC does not appear to have diligently reviewed the available evidence, and did not consult independent experts. The MAC was empowered to review conduct and report conclusions, but instead it brought forward allegations. The Board and the MAC referred the allegations without specifying which CPSO or University policies Dr. Olivieri was alleged to have breached. The action damaged Dr. Olivieri's reputation and imposed a substantial, unwarranted burden of defending herself before two different bodies, without knowing the case she

had to answer. Regardless of the intentions or purpose of these actions, they later were used by Apotex in efforts to discredit Dr. Olivieri and defend the reputation of its drug L1.

54 | Although Apotex’s own interests were served in 1998 when it put forward to regulatory agencies and to Dr. Olivieri’s employers *post hoc* reasons for why it terminated the Toronto L1 trials (alleged protocol violations), these reasons were materially different from the reason given in its own statements made at the time of the terminations in 1996 and during the following year. This was inappropriate conduct by the company.

55 | Apotex made statements to regulatory authorities about the relative significance of the two Toronto efficacy and safety trials (LA-01 and LA-03), and the safety trial at international sites (LA-02), that were contradicted by its own earlier documents. The protocol for the international trial specified that it was a short-term trial, the primary objective of which was to assess the occurrence of known acute-toxicity effects of L1. The information and consent form for patients enrolling in the international trial stated that its purpose was to determine the safety of L1. This nature of the international trial was acknowledged by Apotex’s Vice-President, Dr. Spino in 1996, when he wrote that it was a safety study of short duration (1 year). However, in later submissions to regulatory authorities in 1998, Apotex stated that the short-term toxicity trial at international sites (LA-02) was the pivotal efficacy and safety trial for licencing purposes, and that the randomized comparison trial (LA-01) and the long-term efficacy and safety trial (LA-03) in Toronto were supportive studies to the LA-02 study. We have seen no convincing evidence that would demonstrate why or how the public interest was served by Apotex’s claim that LA-02, rather than LA-01, was the pivotal trial of the drug.

56 | Attempts to discredit Dr. Olivieri and her work were an aspect of Apotex’s 1998 licencing submissions for its drug L1 to regulatory agencies. This information was not disclosed to Dr. Olivieri by the regulators or by Apotex. Subsequent to learning of its existence independently, she was only able to gain access to particulars of Apotex’s allegations against her work through court proceedings in Europe.

57 | Apotex’s attempts to discredit Dr. Olivieri with regulatory agencies, and with other scientists, included allegations that liver biopsy was not an accepted or appropriate diagnostic guide to therapy for transfusion-dependent thalassemia patients, but rather was a needless, risky procedure done by Dr. Olivieri for research purposes. A review of the relevant medical literature shows that this is not the case—liver biopsy is a safe procedure that is necessary to guide appropriate therapy for such patients, and to assess the efficacy and safety of their

iron-chelation treatment. Nevertheless, similar incorrect allegations were later put forward by Dr. Koren and Dr. O’Brodivich to the MAC, with specific reference to biopsies done on some of Dr. Olivieri’s patients in 1997 following identification of the risk that L1 could cause progression of liver fibrosis. The allegations were believed by the MAC.

58 | Dr. Olivieri sought a meeting with Health Canada officials in June 1999 to express concerns regarding Apotex’s licencing submissions. She was accompanied by Dr. Michèle Brill-Edwards who assisted her in her presentation. Shortly afterward, Dr. Brill-Edwards received two letters—one an anonymous letter disparaging Dr. Olivieri and others who were critical of Apotex’s drug L1 and of the HSC administration, and the other a signed letter from Dr. Koren offering her employment in his HSC Division. DNA evidence from envelope of the anonymous letter to Dr. Brill-Edwards identified Dr. Sergio Grinstein, a scientist at HSC and a public supporter of the HSC administration in the L1 controversy, as the author. DNA evidence from the envelope of the signed letter to Dr. Brill-Edwards identified Dr. Koren as the author of the series of anonymous letters against Dr. Olivieri and her supporters sent out in late 1998 and early 1999.

59 | Neither Dr. Olivieri nor the colleagues who tried to assist her during the first two years of the controversy (1996–1998) were aware that the University of Toronto Faculty Association (UTFA) and the Canadian Association of University Teachers (CAUT) could be approached for advice and assistance.

60 | UTFA and CAUT knew of the dispute and its implications for academic freedom and research ethics in August 1998, when it became public, yet they did not offer assistance to Dr. Olivieri until November 1998. However, both associations provided substantial assistance from November 1998 onward, to the present in the case of UTFA, and until this Committee of Inquiry commenced work in September 1999 in the case of CAUT.

61 | Sir David Weatherall of Oxford University and Dr. David Nathan of Harvard University, UTFA, CAUT, and President Robert Prichard of the University of Toronto, were instrumental in bringing about the agreement of January 25, 1999 that resolved the dispute concerning HSC’s removal of Dr. Olivieri from her program directorship. President Prichard has been rightly credited with having played an indispensable role in the mediation process on this occasion, a process that resulted in this very significant agreement.

62 | The agreement of January 25, 1999 also resolved a number of other important matters, including violations of the academic freedom of Dr. Olivieri and her colleagues, Drs. Chan, Durie and Gallie, by HSC through the

issuance of “gag orders” to them on January 6, 1999. Under this agreement, HSC withdrew the “gag orders.”

63 | The agreement of January 25, 1999 provided, for the first time, assurance that HSC would provide legal support for Dr. Olivieri, in the event Apotex took legal action against her and the CMPA declined to support her. This implied a belated acknowledgment by the Hospital that it had responsibilities in the dispute between Apotex and Dr. Olivieri.

64 | Given the Hospital’s previous treatment of Dr. Olivieri, the University, UTFA and CAUT should have made representations to the Hospital for Sick Children in January 1999 in an effort to ensure that Dr. Olivieri would be provided due process in the MAC inquiry. UTFA and CAUT did not do so and we have seen no evidence that the University did so. It became clear a year later that Dr. Olivieri had been very seriously denied due process by the MAC. The University, in particular, had publicly stated in December 1998 that it had a commitment from the Hospital that it would be consulted on actions adverse to Dr. Olivieri in matters arising from findings in the Naimark Report. We have seen no evidence that the University pursued this commitment to ensure it was fulfilled.

65 | Throughout this dispute, during which Dr. Olivieri was publicly and privately criticized by medical administrators of the Hospital for Sick Children, she has had the confidence and support of medical administrators in The Toronto Hospital where she treats adult patients, including Physician-in-Chief Dr. Michael Baker.

66 | Dr. Olivieri’s efforts during the past five years and more to exercise her rights and responsibilities, and to uphold principles of academic freedom and research and clinical ethics, have been at great personal cost to her.

67 | Drs. Chan, Dick, Durie and Gallie have actively supported the principles of academic freedom, research ethics, research integrity and fair procedures during the past several years. They have supported Dr. Olivieri in the exercise of her individual rights during this time. Without their active involvement, events in this case would likely have been still more unfortunate for the upholding of these general principles, and for Dr. Olivieri, than they have been. Their involvement has been at great personal cost to each of them, but they felt moved to intervene when the institutional leadership of the University of Toronto and the Hospital for Sick Children had failed to provide effective support either for the general principles or for Dr. Olivieri.

68 | Officers of the University of Toronto, including President Prichard and Dean David Naylor made substantial efforts during 1999 to mediate disputes between Drs. Olivieri, Chan, Dick, Durie and Gallie, and the Hospital for

Sick Children. Although these efforts have not yet been brought to a successful conclusion, they could still form the basis for resolving a number of outstanding issues.

69 | It is unfortunate the University did not effectively intervene to counter the legal warnings by Apotex or unfair actions against Dr. Olivieri by HSC prior to January 1999, or effectively address certain other relevant matters since then. However, it is the case that without some of the significant interventions the University has made, events in this case would likely have been still more unfortunate for the upholding of these general principles, and for Dr. Olivieri, than they have been.

General

70 | The central issue in both instances of identification of an unexpected risk was an ethical one. A drug manufacturer, Apotex, attempted through legal warnings to impede a clinical investigator and treating physician, Dr. Olivieri, from informing patients and others of the risks. By these actions, Apotex attempted to deprive patients of their right to give informed consent to a treatment that was unproven as to its efficacy and safety, and it thereby acted contrary to the public interest.

71 | The issue of academic freedom is related to the ethical issue: communication through presentations at scientific meetings and through other publications were essential to alert physicians around the world to risks of the drug. Speaking out on the actions of Apotex and on the failures by the Hospital for Sick Children and the University of Toronto to take any effective counter-action (until early 1999), was also important to the public interest.

72 | This case demonstrates the importance to the public interest that universities and their affiliated teaching hospitals act robustly to protect academic freedom, bringing to bear the full weight of their resources in cases where large private corporations attempt to infringe academic freedom.

73 | This case demonstrates the importance to the public interest of ensuring that in hospitals affiliated with universities, hospital staff who hold academic appointments have the right to academic freedom and its protection to ensure their independence.

74 | This case demonstrates the importance to the public interest of ensuring that in hospitals affiliated with universities, inquiries by Medical Advisory Committees into conduct of clinical professors be conducted with standards

of fairness and due process commensurate with the seriousness of the allegations under review.

75 | This case demonstrates the importance to the public interest of ensuring that in hospitals affiliated with a university, staff holding academic appointments in the university have access to grievance and arbitration procedures on all significant matters pertaining to their hospital employment, and that such procedures be comparable to and harmonized with the university grievance and arbitration procedures.

76 | This case demonstrates the importance to the public interest of ensuring that investigators conducting clinical trials do so in the context of strong guidelines, regulations, or legislation, that exist and are enforced to protect investigators' independence, and thus their ability to act in the interests of trial participants and patients.

77 | There are important gaps in the policies and procedures of the Canadian research granting councils and Health Canada to protect public safety in clinical trials. Nationwide rules, and mechanisms for enforcing the rules, to govern relationships among investigators, their institutions and industrial sponsors of clinical trials, are urgently required.

D

Recommendations

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General

1 | All contracts, protocols and investigator agreements for industrial sponsorship of clinical trials should expressly provide that the clinical investigators shall not be prevented by the sponsor (or anyone) from informing participants in the study, members of the research group, other physicians administering the treatment, research ethics boards, regulatory agencies, and the scientific community, of risks to participants that the investigators identify during the research. The same provisions should apply to any risks of a treatment identified following the conclusion of a trial in the event there are patients being administered the treatment in a non-trial setting.

Certain circumscribed confidentiality restrictions may be appropriate, for example, those pertaining to information on the chemical structure, or synthesis of a drug, or its method of encapsulation. However, restrictions on disclosure of risks to patients are not appropriate, subject only to the condition that the investigator believes there is a reasonable basis for identification of the risk. Under the term “risk” we include inefficacy of the treatment, as well as direct safety concerns.

The Hospital for Sick Children & the University of Toronto

2 | The Hospital and the University should address the professional misconduct by Dr. Gideon Koren in putting forward false and seriously neglectful allegations and testimony against Dr. Olivieri to the Naimark Review and the Medical Advisory Committee.

3 | The University and the Hospital should address the academic misconduct by Dr. Koren in regard to his article, “An Investigation Into Variability in the Therapeutic Response to Deferiprone in Patients With Thalassemia Major” in the journal *Therapeutic Drug Monitoring*, volume 21 (1999), pp. 74–81.

4 | The University and the Hospital should investigate the facts and circumstances pertaining to Dr. Koren’s actions in the following matters: his role as senior author of two abstracts presented by an Apotex employee at the 6th International Conference on Thalassaemia and the Haemoglobinopathies held in Malta in April 1997; and his failure to disclose the source or purpose a \$250,000 grant from Apotex in the academic year 1995–1996 for use in 1996–1997.

5 | The University should address the misconduct of Dr. Michael Spino, who holds the status of professor in the Faculty of Pharmacy, in repeatedly violating Dr. Olivieri’s academic freedom.

6 | The Hospital for Sick Children should immediately and publicly withdraw its April 2000 referrals to the College of Physicians and Surgeons of Ontario and the University of Toronto, of the enumerated “concerns” of the Medical Advisory Committee regarding Dr. Olivieri.

7 | Dr. Olivieri should receive redress from the Hospital for Sick Children and the University of Toronto for the unfair treatment she has received, including their lack of support to her in the exercise of her rights and obligations.

8 | Dr. Olivieri should receive redress from the Hospital for Sick Children for the damaging and unfair actions against her by its Medical Advisory Committee and Board of Trustees arising from the MAC proceedings.

9 | Dr. Olivieri, and Drs. Chan, Dick, Durie and Gallie believe that they were subjected to unfair treatment in certain matters of their employment and working conditions, for exercising their right to academic freedom in the matters outlined in this report. In the case of Dr. Olivieri, this was from 1996 onward—in the cases of Drs. Chan, Dick, Durie and Gallie, subsequent to their being identified as supporters of Dr. Olivieri. This Committee of Inquiry did not investigate and address all of these matters. We understand that some concerns of these five scientists were under consideration in the mediation process undertaken by the Dean of Medicine in the fall of 1999, and that other concerns are the subject of grievances lodged with the University of Toronto in late 1998 and augmented since then. Neither the mediation nor the grievance process has yet been brought to a resolution in the ensuing years. These processes should be brought to an expeditious and fair resolution.

Research Ethics Boards

10 | Not only all protocols but also all associated research contracts and investigator agreements should be reviewed and approved by Research Ethics Boards (REBs) to ensure, among other things, that they comply with recommendation 1. The REBs should ensure that the wording of protocols is congruent with their associated contracts and investigator agreements. REBs should have, and should exercise, the power to withhold approval of any proposed study if any of the associated protocols, contracts and investigator agreements contain inappropriate confidentiality clauses.

REBs should be permitted to delegate the authority to conduct reviews of contracts and investigator agreements to the institutional office of research services. However, such delegation should only be done if:

- a) the office is given clear instructions that contracts and investigator agreements must comply with recommendation 1, with the protocols approved by the REB, the ethical standards articulated in the *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS)* and other norms of research ethics; and
- b) there is an annual process of auditing by the REB of a representative sample of contracts and investigator agreements to ensure consistency between the protocols (and ethical standards) and the contracts and investigator agreements.

11 | REBs should ensure that the guidelines in recommendation 10 are understood and followed by all sponsors and investigators. Insertion of the following text in the relevant documents is recommended:

a) *Consent form*

Throughout the research process, you will be given any new information that might affect your decision to participate in the research. In particular, you will be told of any unforeseen risks that may be identified.

b) *Protocol*

No agreements or contracts between researchers and sponsors that limit the right and the responsibility of the researchers to disclose relevant information about unforeseen risks that becomes known in the course of the research, to participants in the study, members of the research group, other physicians administering the treatment, research ethics boards, regulatory agencies, and the scientific community, have been or will be entered into by the researchers.

c) *Investigator agreements / contracts*

If I have concerns about the safety and/or efficacy of the study drug, X, I have the right and the responsibility to disclose relevant information that becomes known to me in the course of the research, to participants in the study, members of the research group, other physicians administering the treatment, research ethics boards, regulatory agencies, and the scientific community.

12 | REBS should review project budgets as well as the research protocols and associated contracts and agreements, in order to ensure that all actual and potential conflicts of interest are managed in an ethical fashion.

13 | REBS should ensure that protocols and related contracts and agreements make express provision for management of patient care in the event of premature termination of a research trial, and should withhold approval of the study until such provision has clearly been made.

14 | REBS should review institutional policies and practices with respect to access to patient records for research purposes to ensure that they are in compliance with the *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS)*.

Universities & Teaching Hospitals

15 | Each Canadian university with a faculty of medicine, and each affiliated health care institution, should put in place the policy in recommendation 1 together with procedures to ensure compliance, and ensure that their REBS comply with recommendations 10–14.

16 | Universities and affiliated teaching hospitals should implement appropriate policies and practices to ensure protection of the right to academic freedom of clinical and other researchers and bioethicists who work in teaching hospitals and who hold academic appointments in affiliated universities. Relevant provisions should be included in affiliation agreements.

17 | Clinical and other researchers, and bioethicists, who are employees of teaching hospitals and who hold academic appointments in the affiliated university, should have access to grievance and arbitration procedures in matters pertaining to their hospital employment, as well as their university employment. The affiliation agreement between a teaching hospital and a university should require that the hospital grievance and arbitration procedures are comparable to, and compatible with, those available to faculty members employed full-time in the university. The affiliation agreement should specify the process with

jurisdiction, and the responsibility for remedies, in matters involving both hospital and university employment.

18 | Teaching hospitals affiliated with universities should put in place a policy of due process in such matters as: removal of administrative office from an employee; Medical Advisory Committee (MAC) investigations into conduct of a staff physician; and disciplinary proceedings. The policy should make clear that adverse MAC recommendations and adverse administrative or Board decisions arising from MAC recommendations are subject to grievance and arbitration.

19 | Provision should be made by each institution for training and briefing new members and Chairs of Research Ethics Boards on matters relevant to their work. This briefing should include familiarization with: the *TCPS* and other relevant legal and ethical norms, guidelines and policies; and accurate information on the status of all active research protocols and recently terminated protocols. REB Chairs should have adequate independence and authority, as well as adequate release time and administrative support, to carry out their mandate to protect the safety of research participants and the public interest.

20 | The nature and importance of scientific independence, academic freedom, and of putting patient safety first in interactions with drug companies or other sponsors of research, should be incorporated into training programs for students in all medical schools and affiliated health care institutions. Students should be made aware of potential conflicts of interest, and of the need and ways to ensure they are managed in the public interest.

AUCC & CAUT

21 | To ensure a united stance and prevent any likelihood of companies moving research projects to institutions with less stringent patient protection, there should be a national, integrated approach for all research done in hospitals affiliated with universities. We recommend that the Association of Universities and Colleges of Canada (AUCC) develop, implement and enforce a policy governing industry-academy relationships that would apply to all faculties of medicine and affiliated teaching hospitals across Canada. Such a policy should include, at a minimum, the provisions outlined in recommendation 1. It should also include guidelines for determining whether a proposed university-industry contract qualifies as academic activity, or as consulting service—with different rules for pricing and overseeing the project for these two categories.

All industry/academy agreements and contracts for health research should be filed with an oversight body established by AUCC for the purpose of ensuring compliance. A surtax should be levied on all industry/academy health research agreements and contracts to fund the activities of this oversight body.

22 | The Association of Universities and Colleges of Canada, the Canadian Association of University Teachers and learned societies should undertake cooperatively an ongoing program to promote academic freedom and the ethical conduct of research. This should include development and implementation of an educational component to be included in all post-graduate and post-doctoral training programs in all fields where research on human subjects is conducted. It should also include an awareness program on these matters for all persons holding academic appointments who work in teaching hospitals affiliated with universities.

23 | The Canadian Association of University Teachers should develop policies and model clauses for grievance and arbitration procedures for medical and health-related faculty members and bioethicists who work in health care institutions affiliated with universities.

24 | The Canadian Association of University Teachers should review and revise its policies on:

a) action in regard to cases of infringement of academic freedom or other important rights or privileges brought to its attention, so as to be in a position to promptly intervene to ensure expeditious access to a fair and effective resolution process;

b) ensuring the independence of Committees of Inquiry into cases that are *prima facie* serious. In the present instance, CAUT agreed to changes to policy at the request of the Committee of Inquiry to ensure its independence.

Granting Councils

25 | In order to help ensure consistency in standards across the country, the Canadian Institutes for Health Research (CIHR), together with the Social Sciences and Humanities Research Council (SSHRC) and the Natural Sciences and Engineering Research Council (NSERC), should impose a requirement that universities and health care institutions receiving any funding from the granting councils have in place the policy in recommendation 1. The requirement should apply to all clinical research projects conducted at these institutions, whether or not such projects are funded by one of the granting councils. A means of ensuring compliance would be the withholding of all CIHR, SSRHC

and NSERC funds where such a requirement is not in place, or is not met, and the Councils should actively monitor compliance.

26 | The *TCPS* should be amended so as to give further explicit and prescriptive direction to REBs on the need and ways to identify and manage conflicts of interest.

Government of Canada

27 | Health Canada should impose a requirement, by statute or regulation, that a clinical investigator neither be asked to, nor agree to limit her/his freedom to disclose any risks identified in every case of an Investigational New Drug application, Emergency Drug Release, or other unproven treatment where Health Canada has jurisdiction.

28 | Health Canada should adopt a policy of establishing an independent inquiry whenever a clinical trial is prematurely terminated as a result of a disagreement between the sponsor and the investigator on identification of a risk.

29 | Health Canada should adopt a policy that whenever a manufacturer makes allegations against the work of a trial investigator in a regulatory submission, the investigator is immediately provided with full particulars by Health Canada and a fair opportunity to respond.

30 | The Government of Canada should ensure that Health Canada has adequate personnel and financial resources to protect the public interest in the regulation of pharmaceuticals.

31 | The Federal Minister of Health should thoroughly review the current regulation of health research in Canada and make changes to, or through, legislation or regulations to ensure that the safety of Canadians is adequately protected, working with Provincial Ministers where appropriate.

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The Committee of Inquiry

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1A | Appointment of the Committee of Inquiry

DR. NANCY OLIVIERI appealed to the Canadian Association of University Teachers (CAUT) for assistance in November 1998. The CAUT subsequently intervened in several matters on her behalf, but the situation remained unresolved. Following a procedure used by CAUT in other unresolved cases, the CAUT decided in 1999 to set up a Committee of Inquiry.* The members of the present Committee of Inquiry were selected and asked to serve on the basis of their expertise and experience. The members were Dr. Patricia Baird (UBC), Dr. Jocelyn Downie (Dalhousie), and Dr. Jon Thompson (UNB) as Chair.

In discussion at their first meetings, the members decided they would serve only on the understanding that they would be independent of positions taken by the CAUT, or any other person or organization. To ensure this independence the committee requested CAUT to agree to special arrangements, reviewed below, to which CAUT agreed. The members of the committee did not seek this appointment and have served without any remuneration.

*The first CAUT committee of inquiry was appointed in 1958, in the case of the dismissal of history professor H.S. Crowe by United College, Winnipeg. The members of that committee were Professors Vernon Fowke (Economics, Saskatchewan) and Bora Laskin (Law, Toronto).

1B | Terms of Reference of this Committee of Inquiry

Re: DR. NANCY OLIVIERI

1. To investigate the sequence of events leading to and subsequent to the crisis at the Hospital for Sick Children and University of Toronto involving Apotex Inc. and Dr. Nancy Olivieri, her colleagues, students, and others who may have been connected with her in this matter.
2. To determine whether there were breaches of medical research ethics and clinical ethics.
3. To determine whether there were breaches of or threats to academic freedom.
4. To determine whether changes in Dr. Olivieri's working conditions during this period impaired her and her colleague's ability to conduct their scientific research and treat their patients.
5. To make any appropriate recommendations.

1C | Committee Members

Dr. Patricia A. Baird

FRSC, OC, OBC, BSc, MD, CM, FRCP(C), FCCMG

Patricia Baird was trained as a pediatrician, then specialized in medical genetics, being Head of the Department of Medical Genetics at UBC for over a decade. She has been a member of numerous national and international bodies, among them the National Advisory Board on Science and Technology chaired by the Prime Minister; the Medical Research Council of Canada (and its Standing Committee on Ethics in Experimentation); and International Ethics Committees. She chaired the Royal Commission on New Reproductive Technologies, which reported several years ago. Since 1991, she has been a Vice-President of the Canadian Institute for Advanced Research. She has received three honorary degrees, the Order of British Columbia, and is an Officer of the Order of Canada. She holds the position of “University Distinguished Professor” at the University of British Columbia.

Dr. Jocelyn Downie

BA, MA, MLitt, LLB, LLM, SJD

Dr. Downie holds a joint appointment in the Faculties of Law and Medicine at Dalhousie University. She holds graduate degrees in bioethics as well as in law and now works at the intersection of ethics, law, and health care. She has served on research ethics boards at a local and national level, and conducts research on research ethics and the regulation of research in Canada. She currently serves on the National Blood Safety council and the Federal/Provincial/Territorial Advisory Committee on Population Health.

Dr. Jon H. Thompson

BSc, MA, PhD

Dr. Thompson is a Professor in the Department of Mathematics and Statistics, University of New Brunswick and Chair of the Department. He was President of the faculty union at UNB in 1979–1981 and chaired the Academic Freedom and Tenure Committee of the CAUT during 1985–1988. He has been involved in the investigation and resolution of disputes at universities across Canada during the past two decades. He was a member of the Independent Committee of Inquiry into Academic and Scientific Integrity appointed by the Board of Governors of Concordia University in 1993–1994. In 1993, he received the James B. Milner Memorial Award for contributions to academic freedom.

Transparency

In the interest of transparency, we note here any interaction committee members have had with persons, institutions, corporations or organizations in this case.

No member of the Committee has any involvement with any drug company, public institution, organization or person that would place her or him in a conflict of interest.

The members of the Committee of Inquiry had no previous acquaintance with each other. Dr. Baird and Dr. Downie had no prior involvement with the CAUT. Dr. Thompson was a member, then chaired the Academic Freedom and Tenure Committee of CAUT during 1985–1988, being as a consequence a member (*ex officio*) of the Board of Directors. He has not held an office in CAUT since that time. He has occasionally been called upon for advice or assistance by CAUT or member associations.

No member of the committee had personally met any of the persons at the centre of the case prior to commencing interviews in the autumn of 1999. Members were aware of the case from media reports. Drs. Baird and Downie had read the Naimark Report prior to serving on this committee.

Drs. Downie and Thompson are graduates of the University of Toronto. Dr. Downie was a summer employee in the Department of Bioethics of the Hospital for Sick Children in 1991. Dr. Downie was a signatory of a letter in the fall of 1998 to University and Hospital officials inquiring as to their institutional policies on matters relating to the case. Dr. Baird has occasionally given general media comments on medical research and the involvement of industrial sponsors.

In September 1998 Dr. Baird was invited by Dr. Arnold Naimark to assist him in the review of the L1 controversy that the Hospital for Sick Children had appointed him to conduct. Dr. Baird declined the invitation, as outlined elsewhere in this report, as she did not feel the arrangement proposed gave her sufficient independence.

1D | Measures to ensure independence

THE CAUT TOOK A POSITION on the case in November 1998 and subsequently attempted to assist Dr. Olivieri. Because of this, the Committee of Inquiry made it a condition of service that measures be put in place to ensure its independence from CAUT. CAUT agreed to these. The first requirements were that the committee be provided with its own office in Toronto, that any research assistants employed would report only to the committee, and that independent legal counsel would be retained. Although the CAUT bore the expenses, these services were under the control of the committee. The CAUT agreed also to refrain from public comment on the case until the committee completed its inquiry and its report was published.

Some of the persons and organizations invited to participate nevertheless declined to accept, citing two reasons: that the committee had been appointed by the CAUT which had taken a position; and that the CAUT policy on inquiries gave it an opportunity to comment on a draft report, and discretion as to whether to publish the completed report. The committee then asked that these provisions of CAUT policy be suspended for the present inquiry, and the CAUT Executive Committee immediately passed formal motions to implement the requested changes. In summary, the requirement for submission of a draft report was eliminated, and the CAUT made a written undertaking to publish the report as submitted and in its entirety. (The texts of the motions are in Appendix D.) These changes were communicated to all persons invited to participate in the inquiry.

The members of the Committee of Inquiry agreed from the outset that any opinions dissenting from the majority would be included in whole in the committee's report, in a separate section of the report written by the dissenting member.

1E | The Inquiry Process

THE COMMITTEE received from CAUT an initial collection of documents pertaining to events that occurred up to early 1999. On the basis of the information in these, as well as the experience each member brought to the Committee, we contacted a large number of persons who had been involved in various ways. These individuals were invited to meet with the Committee, to provide documents, and to suggest the names of others who might have relevant information. Additional persons were contacted as the Committee obtained more information on the case. A list of those contacted is appended, with indications as to whether they participated.

The administrations of the University of Toronto and the Hospital for Sick Children, and a number of individuals declined our invitation to participate. Apotex Inc. also declined. The potential disadvantage of these non-participations was substantially offset by the access the committee obtained to a large quantity of relevant correspondence and other documents originating with the administrations of the University and the Hospital, and Apotex. This included the Naimark Report and most of its documentary base of several hundred documents. That report was commissioned by the Hospital, and the Hospital, the University and Apotex all participated in it. We closely examined the Naimark Report, those of its documents deposited in the HSC library archives, and a number of additional documents relied on by the Naimark Review but not deposited. Our base of information also included many other relevant documents extending over the period 1988–2001 which we closely examined as well. We therefore believe we have relevant information regarding all players in the dispute.

Beginning on October 31, 1999, the committee visited Toronto several times for interviews. Persons interviewed typically brought documents with them and forwarded additional ones later. Additional interviews were conducted by telephone. We also requested additional documentation and received substantial quantities of material in response. In the course of reviewing documents, we occasionally sent copies back to the source with requests for clarification.

On March 26, 2001, pursuant to paragraph 7 of its procedures (see Appendix A), the Committee sent letters to a number of individuals and organizational heads providing, in each case, a summary of information pertaining to their involvement, and inviting comment and further information. Some, but not all, of the recipients of these letters had previously declined to participate and were, through receipt of this letter, again invited to participate and to provide information to the Committee of Inquiry. Some recipients of these letters replied and copies of all replies received are included in Appendix G.

We have sought to have documentary support for our findings and conclusions. To this end, the text of the report is accompanied by an extensive array of endnotes referring to the documents. These documents have been archived.

The inquiry process had two main phases. The investigation phase extended from September 1999 until June 2001. This phase was followed by an evaluation phase where members of the Committee of Inquiry conducted their own separate final review of the relevant information gathered through the investigation phase. This was done to further ensure that each member of the Committee reached her/his own independent conclusions. As will be seen from a reading of this report, each member of the committee reached the same conclusions based on the information reviewed. This is the unanimous report of the Committee of Inquiry.

If at any time any member of the Committee of Inquiry receives evidence which she/he believes contradicts any material aspect of this report, each member of the Committee of Inquiry feels honour-bound to make public any such contradiction.

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Background Information

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2A | The Principal Parties

MANY PERSONS and several organizations have been involved in this case. The following are the principal parties.

Dr. Nancy F. Olivieri is a professor of pediatrics and medicine in the University of Toronto and the physician in charge of the hemoglobinopathy clinics in both the Hospital for Sick Children and The Toronto Hospital. After studying at the University of Toronto (BSc) and McMaster University (MD), she undertook specialised clinical training at hospitals in Hamilton, Toronto and Boston, then postdoctoral research training at the University of Toronto and Harvard University. She is certified by examination as a specialist in two medical disciplines, hematology and internal medicine—by both the Royal College of Physicians and Surgeons (Canada) and the corresponding American Boards. Dr. Olivieri has achieved international recognition as a scientist and clinician, through her many articles in leading journals, and her advances in clinical management of patients with hemoglobinopathies. She has received a number of research awards, including Scientist of the Medical Research Council of Canada (1996-2001). Her stature as an authority on thalassemia is attested to by her review articles in *Blood* and the *New England Journal of Medicine*, which made the treatment protocols she has developed available to physicians elsewhere.

The Hospital for Sick Children (HSC) is one of the world's leading centres for child health care and research. Its specialists have developed medical and surgical techniques that have prolonged and improved the lives of a great many children with serious diseases or injuries. The Hospital is also a centre for advanced training in medical specialties and biomedical research. It is one of the major teaching Hospitals affiliated with the University of Toronto and carries out extensive clinical research.

The University of Toronto is, in a number of respects, Canada's leading university. Its Faculty of Medicine has long been known as a leader in research and training. In addition to its international reputation for education and scholarship, the University has had a significant influence on Canadian society and culture. For instance, the widespread acceptance of the importance of academic freedom in Canada is due, in significant measure, to the efforts of several of its professors from earlier generations: Frank H. Underhill, Bora Laskin, and James B. Milner.

Apotex Inc. is a large and internationally successful manufacturer of generic drugs, with over four thousand employees in Canada and whose products are exported to over one hundred and fifteen countries. Apotex and its subsidiaries, and the Apotex Foundation, have provided funding support to research and other projects in several institutions, including the University of Toronto, the University of Manitoba, and the Hospital for Sick Children.

2B | Others with Prominent Involvement in the Case

Dr. Gary M. Brittenham is now a professor of medicine at Columbia University, but during the L1 trials was at Case Western Reserve University. He is a hematologist and an authority on disorders of iron metabolism. He has won awards for his research and grant support from the National Institutes of Health. Dr. Brittenham developed the only accurate alternative to liver biopsy for the measurement of hepatic iron concentrations, using magnetic susceptibility.

Dr. Gideon Koren is a professor in the Faculties of Medicine and Pharmacy in the University of Toronto. He graduated in medicine in Tel Aviv and later undertook training in Israel and Toronto in pharmacology and toxicology. He is categorized as medical scientist by the Royal College of Physicians and Surgeons (Canada); this is a general categorization that does not connote a specific discipline.* He is a very prolific author, with many articles in pharmacology and toxicology. He has received a number of awards, including being appointed by the Hospital and the University to the CIBC-Wood Gundy Children's Miracle Chair in Child Health Research. He has held a number of administrative positions in HSC, including Associate Director for Clinical Research (1988–1998) and Director of the Division of Clinical Pharmacology and Toxicology (1992–1999).

Dr. Michael Spino is Senior Vice-President, Scientific Affairs of Apotex. Prior to joining Apotex he was a fulltime member of the Faculty of Pharmacy in the University of Toronto. Throughout the events described in this report, he continued to hold the status of professor in the University's Faculty of Pharmacy, while employed by Apotex.

The Toronto Hospital (TTH, also referred to as the Toronto General Hospital) cares for adult patients. Like HSC, it is recognized internationally for its leadership in clinical care, advanced training and research. It belongs to the University Health Network, a group of hospitals affiliated with the University of Toronto.

*Unlike inclusion in the more specific categories, inclusion in this category did not require the passing of an examination in a discipline.

2C | The Hemoglobinopathies: Thalassemia & Sickle Cell Disease

Hemoglobinopathies are inherited disorders of the synthesis or structure of the protein (globin) part of the hemoglobin molecule that enables red blood cells to transport oxygen. Thalassemia and sickle cell disease (SCD) are the most common hemoglobinopathies, and in their severe forms result in premature death, if untreated. They are more prevalent in human populations in parts of the world where malaria is common. Because of Canadian immigration patterns, the HSC and TTH clinics have in total the largest populations of thalassemia and SCD patients of any centre in North America.

The L1 trials involved patients with thalassemia major and we provide an outline of that disease and its treatment. This is important because the HSC Medical Advisory Committee was provided with incorrect testimony on the management and care of thalassemia patients and believed it. This incorrect belief led to some of its allegations against Dr. Olivieri. There was an additional, secondary issue regarding a proposed trial of L1 in treatment of SCD that had not begun, so no patients were involved, that also arose from incorrect testimony.

THALASSEMIA MAJOR. The term thalassemia encompasses many different inherited defects in the genetic structure coding for hemoglobin. The variety of defects results in diverse clinical manifestations of the disease. Thalassemia major (sometimes referred to as β -thalassemia, or Cooley's anemia) arises from defects in the synthesis of the β -globin chains of the hemoglobin molecule. In the severe forms, little or no β -globin is produced, which results in severe anemia and other problems. The disease is fatal in early childhood if untreated.

The accepted treatment of thalassemia major is regular blood transfusion to counteract the anemia. A side-effect of the transfusions is a build-up of excess iron (iron loading) in major organs, notably the heart, liver and endocrine glands. If the iron loading is untreated, these organs progressively fail. Both thalassemia major and iron-loading are very complex conditions to manage clinically. Before the development of an effective treatment for iron loading, a substantial fraction of thalassemia major patients regularly transfused from early childhood did not survive beyond early adulthood.¹ Iron-induced cardiac disease is the most common cause of death in these circumstances; liver disease is another. The latter can also result from the combined effects of iron-loading and infection by hepatitis C virus, a common infection in frequently transfused patients.²

Iron loading is treated by iron-chelation therapy. A drug containing a chemical with an affinity for iron is administered; this extracts excess iron from tissues, which is then excreted. The standard treatment is by the iron-chelating compound deferoxamine, first used to treat iron-loading in 1962. Substantial improvements in its clinical efficacy were achieved in the 1970s by groups headed by M. Barry (London), D.G. Nathan (Harvard) and D.J. Weatherall (Oxford). Unfortunately, this compound cannot be taken by mouth; it must be administered by subcutaneous infusion, driven by a pump. To maintain tissue iron-stores at a safe level, this treatment must be applied for many hours, several days every week. Although onerous, deferoxamine therapy has been proven generally effective when complied with and arrests iron-induced organ damage, such as liver fibrosis. Some patients on this therapy now have lived more than three decades.

Since the serious effects of iron overload begin in early childhood, it is recommended that deferoxamine therapy begin at an early age. It is reasonably safe in most patients when properly administered, but does have several known toxic side-effects, some of particular concern in young, rapidly growing children. During the past decade, Dr. Olivieri and other investigators advanced the effectiveness and safety of deferoxamine therapy through such means as precisely titrating doses for individual patients based on their hepatic iron concentrations. They found that physicians must carefully monitor patients and appropriately adjust the deferoxamine dosages in an effort to balance risks and benefits. In a 1997 review article in the journal *Blood* discussing recent advances in the science and clinical management of thalassemia, Dr. Olivieri and Dr. Brittenham reported:

Significant deferoxamine toxicity can be avoided by regular, direct assessment of body iron burden with regular evaluation of the hepatic iron concentration.^{3*}

In 1995 an international panel of experts on thalassemia convened by the National Institutes of Health (USA) reported:

Accurate determination of the extent of body iron loading has been essential to guide iron-chelation therapy and to monitor its progress in removing iron.⁴

The only accurate measure of body iron burden is hepatic iron concentration (HIC). This is usually determined by chemical analysis of liver tissue obtained by percutaneous biopsy—an invasive procedure, but one established in the medical literature as a safe, reliable and recommended guide to therapy for patients with thalassemia major.⁵ Liver biopsy is normally performed at well separated intervals, typically on an annual basis, unless clinically indicated otherwise. In

*It has been found that the simpler, indirect means of assessing body iron, serum ferritin concentration, is inaccurate and leads to administering deferoxamine at dosages that are too high for some patients.

the early 1980s Dr. Brittenham developed an accurate, non-invasive alternative method for HIC determination, by magnetic susceptometry using a superconducting quantum interference device (SQUID). However, his laboratory in the United States, and another built later in Germany, are the only facilities with the required equipment, so access to this alternative is not widely available.

In the 1997 review article in *Blood*, tables were given showing in detail how the dosages and frequency of administration of deferoxamine should be varied depending on the results of tests, including liver biopsies from which the hepatic iron concentration (HIC) is obtained. The tables also specify at what values for HIC deferoxamine therapy should be started, and when it can safely be interrupted for a time. For example, if the HIC is less than 3.2 mg/g dry weight in a new patient, then the chelation therapy can be deferred, and the patient re-assessed in 6 months. If the HIC is higher than this threshold, then the therapy should be initiated on the standard basis of subcutaneous infusion during 5 nights every week. However, for very high HIC levels the dosage and frequency of application of chelation should be increased.⁶

As is to be expected with such an onerous treatment regime, rates of compliance with deferoxamine therapy vary, especially among teenagers and young adults.⁷ It would be ideal if there were a safe, effective iron-chelation drug that could be taken by mouth. Such a drug would benefit many thousands of patients worldwide. It was hoped that L1 might serve this purpose.

SICKLE CELL DISEASE. SCD results from a structural defect in the β -globin chain that causes distortion and fragility of red blood cells. The disease has many adverse clinical effects, including debilitating and potentially fatal crises. SCD patients may be transfused for specific purposes, such as to relieve crises or in preparation for surgery but, in contrast to patients with thalassemia major, they are not typically dependent on regular transfusions.

3

Policy Context

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3A | Background on Research Ethics & Clinical Ethics

(1) Introduction

RESEARCH ETHICS AND CLINICAL ETHICS

Research ethics is primarily concerned with ensuring that participants in a research study and those affected by the results of the research are protected from unethical research itself, and the consequences of unethical research. The aim is to ensure that research is conducted in a manner that serves the needs of human subjects of research, particular groups of individuals, and society as a whole. Clinical ethics is concerned with ensuring that patients are protected and respected, and that social values are reflected in the policies and practices within health care. Norms for ethical conduct in both contexts have been established by professional bodies, institutions and governments. Both are relevant to the present inquiry because an unexpected risk of the drug L1 was identified in each of the two treatment contexts.

The need to regulate research

Atrocities committed on human subjects by Nazi physicians in the name of scientific research were revealed at the Nuremberg trials,¹ and led to the development of the *Nuremberg Code*, a codification of ethical principles for research involving human subjects.² Codification did not, however, put an end to exploitative research practices. A notorious subsequent instance is the Tuskegee Syphilis Study of 399 African American men with syphilis between 1932 and 1972. When the research participants were enrolled in the study, there was no known effective treatment for syphilis. As new effective drugs were developed (by 1951 penicillin had become standard treatment), they were deliberately withheld from the Tuskegee subjects. The 40-year study ended only when the media exposed the scandal.³

Unethical, harmful, and exploitative human experimentation has been conducted in Canada as well. One such study occurred during the 1950s and 1960s, when at least 80 psychiatric patients at the Allan Memorial Institute in Montréal were used as unwitting subjects in government-sponsored brain-washing studies involving hallucinogenic drugs.⁴

With the rapid growth in drug development by private corporations, clinical trials of new drugs in publicly-funded university teaching hospitals are being funded by corporate sponsors at an increasing rate. This has led to conflicts involving clinical researchers and sponsors. Some companies have attempted to prevent clinical researchers from fulfilling ethical obligations to inform trial subjects, or the scientific community, about risks of the

treatment under study. Similar conflicts have arisen in non-trial settings after identification of an unexpected risk of a treatment, or lack of advantage of an expensive treatment. In one widely-publicized case, Dr. Betty Dong, a clinical pharmacologist at the University of California, showed that an inexpensive generic drug was comparable in efficacy and safety to the brand-name thyroid drug she was studying. The study sponsor, Knoll Pharmaceuticals, then criticized the quality of her work and used legal warnings in an effort to prevent publication of her findings.⁵ (Dr. Dong's case has many similarities with that of Dr. Olivieri, the subject matter of the present report.)

(2) Regulation of research involving human subjects in Canada

LEGISLATION

There is no federal legislation dedicated to the regulation of the conduct of research involving humans. Some pieces of legislation govern aspects of research (e.g., sections of the regulations under the *Food and Drugs Act* apply to pharmaceutical trials),⁶ but no statutes specifically and comprehensively address the regulation of research.

There is a similar legislative vacuum at the provincial/territorial level, with the notable exception of Québec, the only jurisdiction in Canada that has enacted specific legislative provisions regulating activities relating to human experimentation. The *Civil Code* (CCQ) was amended to include specific provisions concerning research in response to concerns that arose during early heart transplantation procedures.⁷

Common law

A pivotal case in Canada is *Halushka v. University of Saskatchewan*.⁸ A university student was told that the researchers were testing an anaesthetic, but not that it was a new and untested drug or that the test required a catheter to be inserted into his heart. He suffered a cardiac arrest, was resuscitated, but suffered serious and irreversible harm. It was through this case that the standard for disclosure of information about risks to prospective research participants was firmly established in Canadian common law.

The case of *Weiss v. Solomon* set a standard of disclosure of even low-probability risks to potential research subjects.⁹ A man enrolled in a study of ophthalmic drops was not informed of all of the risks associated with a particular test. He suffered cardiac failure and died as a result of the test. The man's family sued and both the researcher and the Research Ethics Board (REB) were found liable.

The case that is the subject of this inquiry also involved treatment in a non-trial setting, to which the general common law of contract and tort is also relevant. We obtained an opinion from Professor Emeritus D.A. Soberman (Law, Queen’s University), reproduced in Appendix F. He outlined obligations of the physician in the doctor-patient relationship both in clinical and in trial settings and concluded:

I believe it is clear from the above discussion that a physician is under a legal duty to disclose “material” or “significant” risks, and that failure to do so may well amount to the tort of negligence.

Professor Soberman reviewed the LA-01 trial contract Drs. Olivieri and Koren signed with Apotex with its confidentiality clause giving Apotex the right to control disclosure of trial information during the term of the contract and for one year thereafter (see section 5A). He wrote:

The patient must be given the opportunity to decide whether to proceed or continue with the treatment. In these circumstances, the researcher does not have to establish the complete accuracy of her concern—a risk is a risk, not a certainty—but only that it was not an unreasonable concern.

He added:

In my opinion, it is clear that any term in a contract that prohibits disclosure of information that would amount to the commission of a tort is, to the extent that it does so, illegal and void.

GUIDELINES

National

When the dispute involving Dr. Olivieri and Apotex Inc. began in 1996, the relevant national guidelines were the Medical Research Council (MRC) *Guidelines on Research Involving Human Subjects* (1987),¹⁰ which lacked the force of law. They were also limited in scope, being mandatory only for research funded by the MRC and providing no guidance regarding research contracts with corporate co-sponsors of clinical research under MRC’s university-industry program. Notably, the MRC *Guidelines* did not prohibit contracts with confidentiality clauses that protected the sponsor’s interests and did not protect the interests of trial subjects.

In 1997, the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals For Human Use produced *Good Clinical Practice: Consolidated Guideline* (GCP Guidelines, also known as the ICH Guidelines).¹¹ These guidelines, adopted as policy by the Therapeutic Products Programme (now Therapeutic Products Directorate) of Health Canada, apply to all research on drugs for which the researchers and/or sponsors will seek licensing from Health Canada.

In 1998, the 1987 MRC Guidelines were replaced with the 1998 *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS)*.¹² Like the *MRC Guidelines*, this statement is limited in force—a policy statement not backed by legislation—but its scope is broader than the MRC Guidelines, since it applies to *all* research (not just research funded by the Councils) conducted at institutions that get any funding from the three Councils. The MRC was folded into the Canadian Institutes of Health Research (CIHR) in 2000; the other two federal government research granting councils are the Social Sciences and Humanities Research Council (SSHRC), and the Natural Sciences and Engineering Research Council (NSERC). It establishes that the three Councils “will consider funding (or continued funding) only to individuals and institutions which certify compliance with this policy regarding research involving human subjects.”^{*13}

International

Many Canadian researchers participate in multi-centre trials where there are sites in Canada as well as in the United States. The research (including the protocol and the consent) will therefore frequently be designed to meet the US requirements. In the United States, federal regulations under the title Public Welfare and Human Services (“Protection of Human Subjects”) establish basic requirements for experimentation and research involving human subjects.¹⁴ These regulations are supplemented by state legislation and the requirements of local institutions. Research testing of drugs must also comply with Food and Drug Administration (FDA) regulations.¹⁵

Approximately 19 international codes and other instruments relate to research involving human subjects. The most widely adopted are the *Declaration of Helsinki*, first adopted by the World Medical Association in 1964 and most recently revised in October 2000,¹⁶ and the *International Ethical Guidelines for Biomedical Research Involving Human Subjects*, promulgated by the Council of International Organizations of Medical Sciences in collaboration with the World Medical Association in 1993.¹⁷ Although these guidelines have no direct legal force in Canada, they tend to establish ethical norms against which the conduct of research will be judged (for example, in a tort action against a researcher).

Conclusion

*The MRC was folded into the Canadian Institutes of Health Research (CIHR) in 2000; the other two federal government research granting councils are the Social Sciences and Humanities Research Council (SSHRC), and the Natural Sciences and Engineering Research Council (NSERC).

The regulatory framework for research involving humans in Canada is fragmented and rather loose. There is some guidance for the conduct of researchers and for Research Ethics Boards (described below), but much of the framework is seriously deficient. In particular, there is little guidance for the conduct of corporate sponsors of clinical research, to ensure that they act in the public interest, and insufficient means and efforts made to ensure compliance with existing guidelines.

(3) Ethics review of proposed research projects involving human subjects in Canada

Research ethics reviews are conducted by Research Ethics Boards (REBs) generally established at the level of individual institutions (e.g., hospitals and universities). The procedure for ethics review of a clinical research project is broadly similar in REBs throughout Canada. Before researchers commence a study involving human subjects, they first must submit a research protocol—describing the project's proposed purpose, methodology, safety precautions, and informed consent form for patients—to the REB of the institution or facility. The REB evaluates each protocol's ethical and scientific acceptability, then either accepts the protocol, or approves it with specified modifications, or rejects it altogether.¹⁸ The REB retains jurisdiction over the research for as long as the research trial continues. Thus, for example, all changes to the protocol or patient consent form must be approved by the REB, which must be informed of all serious adverse events and changes in information about the potential harm/benefit ratio of the research intervention must also be reported to the REB.

(4) Guidelines relevant to this case

The focal points in the L1 controversy were events that occurred in May 1996 and in February 1997. Until May 1996 there were two trials of the drug L1 in Toronto. One (termed LA-01), a randomized comparison trial jointly sponsored by MRC and Apotex, was covered by the MRC *Guidelines*. The other (termed LA-03 after Apotex became involved in 1993) was a long-term trial that began in 1989, with MRC as sole sponsor until 1993. MRC sponsorship for the long-term trial ended in 1993, and in 1996 (when the dispute began) the sole sponsor for this trial was Apotex, so the MRC *Guidelines* did not apply to the LA-03 trial. Both research trials took place at the Hospital for Sick Children where the investigators held clinical appointments; the researchers were also faculty members at the University of Toronto. Therefore both trials were covered by the research policies of the University of Toronto and the Hospital for Sick Children. The MRC *Guidelines* and the institutional policies required that, in the event an investigator

identified a risk, it be disclosed to the REB which would then decide the subsequent course of action. In early 1996, Dr. Olivieri identified a risk in data of the (non-MRC) LA-03 trial and, pursuant to institutional policies, disclosed it to the REB.

The dispute arose in May 1996, after the Chair of the REB directed Dr. Olivieri to revise the patient information and consent forms to reflect the new information, and Apotex then terminated both trials and issued legal warnings to Dr. Olivieri in an effort to prevent her from complying with the REB directive.

In June 1996 a new arrangement was agreed upon, under the Emergency Drug Release (EDR) program of Health Canada. Some patients who had been enrolled in the LA-01 and LA-03 trials—those for whom the drug was seen to be beneficial and who wished to continue on it knowing of the new risk—were continued on the drug as patients of Dr. Olivieri, in a non-trial setting. Since this treatment arrangement was not a research trial, the REB had no jurisdiction, REB approval was not required, and MRC *Guidelines* did not apply. From this time forward, the relevant standards were national and international ethical norms for treating physicians and the Canadian *Food and Drugs Act and Regulations* (in particular, C.08.010).¹⁹ In February 1997, Dr. Olivieri identified a second risk of the drug which she disclosed to patients, as required under national and international ethical norms for treating physicians. Further disputes developed when Apotex attempted to prevent her from making wider disclosure, and the Physician-in-Chief of the Hospital for Sick Children incorrectly alleged that she had failed to comply with an alleged obligation to disclose the second risk to the REB.

(5) The current situation in Canada on the relevant research ethics issues

In order to draw conclusions about changes to the regulation of research needed to prevent recurrences of events such as those discussed in this report, we outline the *current* standards for research involving human subjects. In 1998, subsequent to the events that are central to this case, new guidelines were introduced in the form of the *Tri-Council Policy Statement: Ethical Conduct For Research Involving Humans (TCPS)*.²⁰ Although not applicable at the time, because we are concerned to draw lessons from the case, we review strengths and weaknesses of the current policy, with a view to making recommendations for further improvements.

THE APPLICATION OF RESEARCH STANDARDS

The *TCPS* governs research funded by the three national funding Councils (SSHRC, NSERC, and CIHR—formerly MRC) as well as research not funded by the Councils but conducted at institutions that receive (or would like to receive) funding from the Councils.

Research conducted at institutions or by individuals who do not receive funding from the Councils is not covered by the only comprehensive document purporting to set standards for the conduct of research involving humans in Canada. The increasing number of privately funded and conducted research trials remain largely unregulated. This is a matter of serious and growing concern, and should be addressed by appropriate government departments and agencies.

ACTIVITIES REQUIRING REVIEW BY AN REB

Research is defined broadly, as “a systematic investigation to establish facts, principles or generalizable knowledge.”²¹ Under the *TCPS*, research involving humans requires review unless exceptions (not relevant to the issues in this case) apply. Clinical trials require ethics review.²² Patient record reviews for research purposes also require ethics review, if identifying information is involved.²³ Although clinical trials conducted in institutions under the ambit of the *TCPS* receive ethics review, it is not clear that all record review research (also referred to as chart review research) are getting ethics review. REBs should review institutional policies and practices with respect to access to patient records for research purposes to ensure that they are in compliance with the *TCPS*.

Responsibilities

a) Researchers

The MRC *Guidelines* section on responsibilities of researchers fell away in the transition to the *TCPS*. However, comments relevant to researchers’ responsibilities occur throughout the text of the *TCPS*.²⁴ Those responsible for the *TCPS* should consider reintroducing a clear and concise section in the *TCPS* on the responsibilities of researchers.

b) Institutions

According to the *TCPS*, the institution should:²⁵

- delegate authority to a properly constituted REB “through the institution’s normal process of governance”
- make clear the jurisdiction of the REB and its relationship to other relevant bodies or authorities

- ensure that REBS have the appropriate financial and administrative independence to fulfill primary duties
- respect the authority delegated to the REB

c) The research granting councils

In the move from the MRC *Guidelines* to the *TCPS*, the explicit statement on the responsibilities of the granting councils moved to a statement of commitment and wishes:

This joint policy expresses the continuing commitment by the three Councils to the people of Canada, to promote the ethical conduct of research involving human subjects.²⁶

In discharging our mandates, the Councils wish to promote research that is conducted according to the highest ethical standards.²⁷

This change is troubling as it means the responsibility for monitoring “local procedures and practices in ethics review”²⁸ and monitoring “the functioning of the REBS which review the work that it funds”²⁹ has dropped away, replaced by a self-reporting system with no apparent checks. The Councils will “consider funding (or continued funding) only to individuals and institutions which certify compliance with this policy regarding research involving human subjects,”³⁰ but no monitoring by the Councils is built into the system. The Councils should acknowledge and meet their responsibility to monitor compliance with the *TCPS* at institutions receiving Council funding for research.

Review of research contracts and/or investigator agreements

The *TCPS* does not impose a requirement on REBS to review contracts or investigator agreements related to clinical research projects they are assessing, and budgets for clinical trials are to be reviewed only to “assure that ethical duties concerning conflict of interest are respected.”³¹

Many, if not most, REBS reviewing research protocols do not review contracts and/or investigator agreements. This is an important omission since, although the research protocol itself may contain no limit on disclosure of information, the corresponding contract or investigator agreement may contain an extremely restrictive confidentiality clause (e.g., no disclosure of any information without the prior express permission of the sponsor in writing). If the REB does not review the contracts and agreements associated with a research project, then the REB may in effect approve unethically conducted research. This is not a hypothetical concern. Within the past two years, protocols have been submitted to REBS which mention side contracts between the sponsor and the researchers, but the contracts have not been provided to the REB. It is then stated that insofar as these contracts are inconsistent with the

protocol, the contracts govern. If these REBs approved such protocols without reviewing the contracts, research could proceed with unacceptable limits on the ability of researchers to disclose new risks to research participants during the course of the trial.

REBs should either review all contracts and investigator agreements, or should delegate the authority to do so to the institutional office of research services. Such delegation should only be done if:

a) the office is given clear instructions that contracts and investigator agreements must be consistent with the protocols approved by the REB or the ethical standards articulated in the *TCPS* and other norms of research ethics; and

b) there is an annual process of auditing a representative sample of contracts and investigator agreements to ensure consistency between the protocols (and ethical standards) and the contracts and investigator agreements.

Neither REBs nor institutional offices of research services should approve contracts or agreements with confidentiality clauses that could be used to prohibit a researcher from disclosing risks to trial subjects, other clinicians administering the treatment, the REB, regulatory agencies and the scientific community.

Disclosure of information about potential harms and benefits

Researchers must disclose all foreseeable harms and benefits of research participation to trial participants and prospective participants, as well as all new information about potential harms and benefits to the participants as it becomes available. The *TCPS* states:

Researchers shall provide, to prospective subjects or authorized third parties, full and frank disclosure of all information relevant to free and informed consent. Throughout the free and informed consent process, the researcher must ensure that prospective subjects are given adequate opportunities to discuss and contemplate their participation. Subject to the exception in Article 2.1(c), at the commencement of the free and informed consent process, researchers or their qualified designated representatives shall provide prospective subjects with the following:

...

(c) A comprehensible description of reasonably foreseeable harms and benefits that may arise from research participation, as well as the likely consequences of non-action, particularly in research related to treatment, or where invasive methodologies are involved, or where there is a potential for physical or psychological harm;

(d) An assurance that prospective subjects are free not to participate, have the right to withdraw at any time without prejudice to pre-existing entitlements, and will be given continuing and meaningful opportunities for deciding whether or not to continue to participate;

...

Article 2.4(d) also requires that researchers specifically ascertain continuing consent from subjects on the basis of new information.³²

REBS should ensure that these guidelines are understood and followed. Insertion of the following text within any research participant consent form would help to make the requirements clear:

Throughout the research process, you will be given any new information that might affect your decision to participate in the research. In particular, you will be told of any unforeseen risks that may be identified.

Confidentiality agreements

By implication, the *TCPS* prohibits the type of restrictive confidentiality agreements seen in this case. Article 2.4(d) requires that researchers must provide prospective subjects:

[a]n assurance that prospective subjects are free not to participate, have the right to withdraw at any time without prejudice to pre-existing entitlements, and will be given continuing and meaningful opportunities for deciding whether or not to continue to participate.³³

The requirement that researchers “specifically ascertain continuing consent from subjects on the basis of new information”³⁴ implies that restrictive confidentiality agreements violate researchers’ duties and the *TCPS*.

The *TCPS* is not as prescriptive with regard to dissemination of research results beyond participants, and there is no article (the more prescriptive parts of the *TCPS*) regarding publication bans. The *TCPS* acknowledges problems but says only:

Researchers and REBS may exert pressure to alleviate this deficiency in the dissemination of research results by resisting publication bans proposed in research protocols, on the basis of ethical obligations of truthfulness and the integrity of research. Research journalists, journal editors, members of editorial peer review boards, sponsors and regulators should address this as an issue of scientific and ethical urgency.³⁵

Inappropriately restrictive confidentiality agreements in sponsored research contracts and/or investigator agreements continue to be common practice in Canada and the USA. The following illustrative examples are selected from contracts and investigator agreements proposed to researchers in Canada by major pharmaceutical manufacturers in Fall 2000.

Example 1:

All data generated from this study are the property of the X [the sponsor] and shall be held in strict confidence along with all information furnished by X and Y. Independent analysis and/or publication of these data by the investigator or any member of his/her staff is not permitted without prior written consent of X. Written permission to the investigator will be contingent on the review by X of the statistical analysis and manuscript and will provide for nondisclosure of X's confidential or proprietary information.

Example 2:

All information developed as a result of the study ..., including but not limited to the case reports, “Confidential Information” which is the sole and exclusive property of Z [the sponsor] during the period of this agreement and subsequent thereto. A [the team of research investigators] agrees not to disclose Z’s Confidential Information to any person, except [members of] A, members of the IRB [REB] or, as required, to [the regulators], without the prior written consent of Z, and further agrees to take all reasonable precautions to prevent the disclosure by [any] investigator and the IRB [REB] of Z’s Confidential Information to a third party.

Example 3:

“Confidential Information” ... means information disclosed to, acquired by or otherwise known by B [the investigator], as a consequence of evaluation of documentation, or otherwise, by B for C [the sponsor], including all information gathered or developed by B.... B acknowledges and agrees that all Confidential Information is and shall be the sole and exclusive property of C and, as permitted hereunder, shall be held in the strictest confidence by B at all times. B shall only use the Confidential Information for the purpose of professional consultation in the context of this Agreement and shall not, directly or indirectly, use, disseminate, dispose, communicate, divulge, reveal, publish ... any Confidential Information. B shall only disclose the Confidential Information on a “need to know” basis and only with the express written consent of C. Further, B shall provide to C and maintain a current list of all individuals who have been permitted access to the Confidential Information. B acknowledges that damages may be an inadequate remedy for breach of this Agreement and B hereby consents to C seeking and obtaining injunctive or other equitable relief in respect of the provisions thereof. ... This Agreement shall enure to the benefit of and be binding upon the respective heirs, executors, administrators, successors and assigns of each of B and C.

REBS should refuse to approve protocols, contracts and investigator agreements that contain confidentiality clauses that interfere with the researchers’ right and responsibility to report unforeseen risks to research participants, REBS, regulators, and other researchers and/or clinicians using the trial drug. They could, for example, insist upon the insertion of the following text at the end of any confidentiality clause found in protocols, contracts, and investigator agreements:

Protocol

No agreements between researchers and sponsors that limit the right and responsibility of the researchers to disclose relevant information about

unforeseen risks to research participants, REBs, regulators, and other researchers have been or will be entered into by the researchers.

Investigator contracts / agreements

If I have concerns about the safety and/or efficacy of the study drug, X, I have the right and the responsibility to disclose relevant information that becomes known to me in the course of the research to participants, other investigators, other clinicians administering the treatment, Research Ethics Boards, regulatory agencies, and the scientific community.

Academic freedom

The *TCPS* directly addresses the issue of academic freedom and acknowledges its central role in research:

Researchers enjoy, and should continue to enjoy, important freedoms and privileges. To secure the maximum benefits from research, society needs to ensure that researchers have certain freedoms. It is for this reason that researchers and their academic institutions uphold the principles of academic freedom and the independence of the higher education research community. These freedoms include freedom of inquiry and the right to disseminate the results thereof, freedom to challenge conventional thought, freedom from institutional censorship, and the privilege of conducting research on human subjects with public monies, trust and support.”³⁶

Conflicts of interest

The *TCPS* addresses conflicts of interest involving researchers, REB members and the institutions in the following articles:

4.1 Researchers and REB members shall disclose actual, perceived or potential conflicts of interest to the REB. REBs should develop mechanisms to address and resolve conflicts of interest.

7.3 REBs shall examine the budgets of clinical trials to assure that ethical duties concerning conflict of interest are respected.

The *TCPS* also explicitly recognizes the fact that institutions may have “a strong interest in seeing a project approved before all ethical questions are resolved.” The *TCPS* suggests:

the public trust and integrity of the research process require that the REB maintain an arms-length relationship with the parent organization and avoid and manage real or apparent conflicts of interest.³⁷

Although the *TCPS* places the onus on REBs to identify and resolve conflicts of interest, further guidance should be provided on the nature and means of identifying and managing the conflicts in issue. For instance, substantial grant funds to individuals or to institutions, or substantial donations to institutions, may constitute just as much a source of conflicts of interest as

equity holdings in companies or consultancy fees.³⁸ REBs need to access *all* relevant financial data in order to determine whether conflicts of interest may be compromising the integrity of researchers, institutions and the research itself.

REBs should review project budgets and related documents and agreements, as well as the research protocol, in order to ensure that all actual and potential conflicts of interest are managed in an ethical fashion. The *TCPs* should be amended so as to give further explicit direction to REBs on the need and ways to identify and manage conflicts of interest.

3B | Background on Academic Freedom

The preservation of academic freedom is ... an issue of pressing and substantial importance. [La Forest J., writing for the majority of the Supreme Court of Canada (1990)³⁹]

Our Nation is deeply committed to safeguarding academic freedom, which is of transcendent value to all of us and not merely to the teachers concerned. [Brennan J., writing for the majority of the Supreme Court of the United States (1967)⁴⁰]

The university's pre-eminent obligation is to ensure the academic freedom of all of its members, wherever they work. [President Prichard, University of Toronto (1998)⁴¹]

Academic Freedom. Widespread public appreciation of the importance to society of academic freedom for individual professors began to emerge in Canada only in the 1960s, following developments in the United Kingdom and especially the United States. Our current understanding emphasizes two aspects: institutional autonomy and individual freedom of inquiry. This is reflected in the policy statements on academic freedom both of the Canadian Association of University Teachers (CAUT) and the Association of Universities and Colleges of Canada AUCC).⁴² UNESCO adopted a similar set of recommendations in 1997. The recent Canadian *Tri-Council Policy Statement for Ethical Conduct of Research Involving Humans* included academic freedom as a guiding principle and referred to the CAUT, AUCC and UNESCO statements.⁴³

In Canadian universities, the definitions of academic freedom for individuals are similar in scope and principle. The definition at the University of Toronto is typical:

[A]cademic freedom is the freedom to examine, question, teach, and learn, and it involves the right to investigate, speculate, and comment without reference to prescribed doctrine, as well as the right to criticize the University and society at large. Specifically, and without limiting the above, academic freedom entitles faculty and librarians to:

- a) freedom in carrying out their activities;
- b) freedom in pursuing research and scholarship and in publishing or making public the results thereof; and
- c) freedom from institutional censorship. Academic freedom does not require neutrality on the part of the individual nor does it preclude commitment on the part of the individual. Rather academic freedom makes such commitment possible.⁴⁴

Evolution of the concept and its acceptance. Academic freedom has come to be seen as important to the well-being of society through the actions

of courageous individuals, and the influence of those who supported these individuals or the principles involved. A few instances were especially significant in this evolution.

In 1894 a prominent economist R.T. Ely was subjected to dismissal proceedings at the University of Wisconsin, for promoting rights for trade unions. He had many influential supporters across the country and, as a result of their making the case, the Board of Regents not only acquitted him but issued a ringing endorsement of academic freedom. However, elsewhere in the United States professors continued to be harassed or dismissed for challenging the established intellectual or social order. In response, the philosophers John Dewey and Arthur O. Lovejoy and others founded the American Association of University Professors (AAUP) in 1915. This organization gained widespread acceptance for its “1940 Statement of Principles of Academic Freedom and Tenure.”⁴⁵ However, the vulnerability of upholding this was demonstrated when the organization effectively collapsed under the pressure of McCarthyism in the 1950s,⁴⁶ and it did not flourish again until some years later.

Two of the most significant academic freedom cases in the English-speaking world were the dismissals of Bertrand Russell, from Trinity College, Cambridge in 1916, and from the College of the City of New York in 1940. Their consequences helped to extend the boundaries of academic freedom beyond the freedom of professors to communicate on subjects in which they are formally trained—and demonstrated that eminence in research will not by itself ensure that the academic freedom of an individual will be defended by his or her university.

Russell, an outspoken critic of government war policy throughout WWI, was among the best known and most highly regarded intellectuals of the time and, as the grandson of one of Queen Victoria’s prime ministers, enjoyed high social standing. In 1916 he was convicted and fined for distributing an anti-conscription leaflet, and then summarily dismissed by Trinity’s governing council. For an even sharper criticism of government war policy in 1918 he was given a second conviction and a six months’ prison term. All nineteen Fellows of Trinity who had survived active duty during the war supported Russell, together with their senior colleagues Rutherford, Hardy and Eddington.⁴⁷ He was offered reinstatement by Trinity after the war and his release from prison.

Russell’s controversial views on social issues so outraged many citizens of New York that he was dismissed even before he arrived to take up a new post at the College of the City of New York (CCNY) in 1940. Those campaigning against his appointment included Episcopalian Bishop Manning, the Catholic Daughters of America, the Hearst press and most Democratic politicians in the city. Prominent among Russell’s defenders were Albert Einstein and John

Dewey.⁴⁸ In 1950, Russell was awarded the Nobel Prize for Literature, and he later observed that among the writings for which he was now celebrated were those for which he had been denounced in New York.⁴⁹

There were similar events in Canada. Several outstanding academics of the 1930s, Frank Underhill (Toronto), and Frank Scott, Leonard Marsh and Eugene Forsey (all of McGill) suffered employment sanctions for their ideas on social welfare and their social activism. Underhill had also suggested that Canada should strengthen ties with the United States, and this so incensed such British Empire supporters as Ontario Premier Mitchell Hepburn and the editors of the Toronto *Telegram* that Underhill might have been dismissed, had not senior officials in the federal government intervened on his behalf.⁵⁰

These examples illustrate why it is in the public interest that professors have the right to challenge the received wisdom or the established order. They also demonstrate that, in the absence of structures to protect this right, the only recourse is reliance upon influential supporters—and, as in the second Russell case, this may not be sufficient.

Protections for Academic Freedom. University autonomy is essential to protection of academic freedom for individuals. In Canada this is provided through the provincial legislative acts of incorporation of universities—which, although state supported, enjoy a large measure of autonomy. Cases such as the above showed that this was not sufficient to protect academic freedom for individuals: administrations or boards of governors did not always act to ensure this. Collective action by the academic community was required.

The Canadian Association of University Teachers had been formed in the late 1940s and became involved when history professor Harry Crowe was dismissed by United College in Winnipeg in 1958, for remarks critical of policies of the college Principal. In response to an appeal from professors at Queen's University on behalf of Professor Crowe, the CAUT set up its first committee of inquiry, consisting of Professors Vernon C. Fowke (Economics, Saskatchewan) and Bora Laskin (Law, Toronto). Their efforts, based on procedures adapted from the AAUP, spurred the CAUT and many of its local associations to become active in protecting academic freedom.

The Fowke-Laskin report⁵¹ stressed the need for an effective concept of tenure as the means for protecting academic freedom for individuals. Professor Daniel A. Soberman's 1965 report for CAUT argued that tenure would only be legally effective if there were formal procedures for granting or denying it, and for revoking it (dismissal).⁵² He also emphasized the importance of fair hearings. Over the next decade, as university governance was democratized, terms and conditions of employment, including tenure

procedures, were formalized and faculty associations began to operate increasingly in the manner of trade unions.

By the early 1970s matters such as academic freedom, the granting of tenure, and dismissal were grievable and arbitrable at several universities, establishing basic procedural fairness. By the late 1980s, a wide range of employment matters were subject to grievance and arbitration procedures at all universities in Canada. By 1990, this evolution had advanced to the point where the Supreme Court of Canada observed that, in matters involving actions by a faculty member's university employer:

Tenure provides the necessary academic freedom to allow free and fearless search for knowledge and the propagation of ideas.⁵³

It is important to note that *The Canadian Charter of Rights and Freedoms* does *not* protect academic freedom. The majority of the Supreme Court of Canada decided that the *Charter* does not apply to university employment matters—"universities do not form part of the government apparatus"⁵⁴—hence the Court's emphasis on the importance of tenure. By contrast, in a recent case involving public statements by two employees of Health Canada, Drs. Margaret Haydon and Shiv Chopra, the Federal Court of Canada quashed disciplinary action by the Associate Deputy Minister. In a decision dated at Ottawa, September 5, 2000, Justice Danièle Temblay-Lamer found that, in the circumstances of this case, the statements by the two government employees were protected from employment sanctions by "the freedom of expression as guaranteed by the *Charter*."

The current importance of academic freedom. Rapid expansion of the university system across Canada in the 1960s came with the transfer of large amounts of federal funding to the provinces. Much of the expansion was in fields such as science, engineering and medicine, where teaching and research are expensive. Grant funding to individual researchers increased as well, enabling development across the country of fundamental research over a broad spectrum of fields. However, over the past two decades, the federal government has steadily reduced funding to the provinces for universities, and this pace of reductions was accelerated in the 1990s, until just recently. At the same time, there was increasing governmental encouragement to researchers to form partnerships with corporations. Commercial interests of sponsors in research findings have the potential to cause distortions of various kinds, unless safeguards are in place.

A research area of particular concern is medicine, where the academic freedom of clinician-researchers is a matter of immediate societal interest because the health of human subjects is involved. The sometimes conflicting goals of sponsors and clinician-researchers mean that the public interest and patients' welfare may not be put first. However, at many universities, clinical research professors have not fully benefitted from advances in procedural protection for fundamental rights enjoyed by their colleagues in other faculties. For a variety of reasons, clinical professors at many universities do not have effective grievance and arbitration procedures for certain aspects of their hospital employment. The universities and their affiliated teaching hospitals have a special responsibility on behalf of the public interest to take actions, and to make policy changes, that ensure the academic freedom of clinical research professors is protected.

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3C | Due Process & Grievance Procedures

PROMINENT FEATURES of the L1 controversy are the lack of an adequate grievance procedure, and of due process in important matters affecting employment status at the Hospital for Sick Children. The Hospital's summary removal of Dr. Olivieri from her program directorship in January 1999 resulted in the intervention of outside parties and the President of the University of Toronto to resolve this and other issues. This event demonstrates the vulnerability of individuals where mechanisms ensuring due process are lacking, and the extraordinary efforts required to obtain redress in the absence of grievance procedures. The lack of an adequate grievance procedure has also meant that some HSC staff, including Dr. Olivieri, have had to engage private legal counsel even for the types of employment disputes that commonly occur in large institutions. In such circumstances, disputes can be prolonged—and, as in the present case, more likely to become inflamed.

Grievance and arbitration procedures. Teaching hospitals affiliated with universities should establish a grievance procedure for full-time medical and scientific staff who are professors in the university, under which significant matters pertaining to terms and conditions of employment are grievable, and arbitrable. Access to arbitration or an equivalent procedure is essential, both to bring disputes to a conclusion, and to serve as a restraint on both parties. The grievance and arbitration procedure for such hospital staff should be comparable to that available to full-time faculty in the affiliated university. The affiliation agreement between university and hospital should specify which procedure (university or hospital) is to be used in cases where the dispute involves work relating to both university and hospital responsibilities.

Since the 1970s a body of jurisprudence pertaining to university employment has developed and many arbitrators have become accustomed to particular features of universities, such as the need to maintain high academic standards through peer review. What arbitration has brought to the university sector is an emphasis on the provision of due process and on the importance of reasonableness in decisions, as well as a means for final and binding resolution. These considerations are also relevant in teaching hospitals.

Dr. John Evans, a former President of the University of Toronto and a member of the Board of the HSC Foundation, called attention to these and other matters in a letter to this Committee of Inquiry in November 1999:

Specifically in the case of teaching hospitals it is my opinion that the following goals are extremely important:

- Develop and effectively disseminate policies and clear guidelines in such areas as ethical conduct of research, ownership of intellectual property, acceptance of research contracts, third party funding and industry relationships.
- Seek maximum compatibility of hospital and university policies governing professional staff appointed to both the university and its affiliated hospital.
- Put in place appropriate policy and instruments of conflict resolution recognizing the special circumstances of clinical faculty members and the inadequacy of labour relations grievance procedures in existence in most hospitals to deal with important issues facing professional teaching and research staff employed by and working at teaching hospitals.

I believe it is incumbent on all teaching hospitals to achieve a high degree of compliance with these types of goals. It is my impression that the Hospital for Sick Children appreciates the importance of these goals and is committed to putting them into practice.⁵⁵

The Naimark Report also addressed these issues, including the inadequacy of dispute resolution procedures in the Hospital for Sick Children. It recommended consideration of “the need for a grievance policy specifically designed for professional and scientific staff,”⁵⁶ and it suggested grievance procedures available in universities could provide models.

The University of Toronto and the Hospital for Sick Children have made progress in some of the areas identified by Dr. Evans and by the Naimark Report, but much remained to be done by the institutions at the time the present report was completed in 2001. For instance, although HSC established an elaborate mediation procedure for dispute resolution in April 2000, it has not yet established an adequate labour relations grievance procedure.

Inquiries by medical advisory committees into conduct. This case demonstrates the need for fairness in proceedings of medical advisory committees in teaching hospitals. This means that, whenever an allegation or adverse information about a physician has been received by a medical advisory committee, and the committee intends to consider such material in a review of conduct, the allegations and information must be disclosed, in full, and in a timely manner, to the individual concerned. That individual must also be given a fair opportunity to respond, and the option of representation by legal counsel in all aspects of the review. Recommendations by medical advisory committees and any resulting actions that may adversely affect a physician’s hospital privileges, employment status, or medical reputation, should be subject to grievance and arbitration.

Procedures of government regulatory agencies. This case demonstrates also that when a drug manufacturer makes serious allegations against a clinical investigator in licencing submissions to a government regulatory agency, the agency should promptly inform the investigator and provide a fair opportunity to respond. Such agencies are charged with protecting public safety and, therefore, should undertake to determine the truth of the matter. The Canadian *Food and Drugs Act* and *Regulations* require manufacturers to submit complete and correct information, and the Health Protection Branch of Health Canada has the responsibility to ensure this. Health Canada should, in the public interest, put in place through legislation, regulations or policy change, a requirement that in such instances the Health Protection Branch must promptly inform the investigator of allegations and provide the investigator with a fair opportunity to respond.

4

*The Context of
Associations Between
Apotex Inc. & the
University of Toronto*

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(1) Associations

Dr. Olivieri and Dr. Koren, the investigators for the two Toronto deferiprone (L1) trials, are professors of medicine in the University of Toronto. The principal sites for both trials were two of the University's affiliated teaching hospitals, the Hospital for Sick Children (HSC) and The Toronto Hospital (TTH), and the Chair of the University's Department of Pediatrics approved the investigators' applications to the Medical Research Council (MRC) for funding. Dr. Spino, Apotex's Vice-President for Scientific Affairs, is a professor of pharmacy in the University. Wider associations between Apotex and the University pre-dated Apotex's sponsorship of these trials, and continued after the company terminated both trials in 1996. These associations form part of the context for Apotex sponsorship of the trials and the controversy that followed their termination.

(2) A possible major donation by Apotex

In the fall of 1998, following the extensive media coverage of the L1 controversy and the establishment of the Naimark Review by HSC, University-Apotex associations were discussed in the University's governing bodies. President Robert Prichard outlined them in a meeting of the Academic Board on October 8, 1998:

The President commented that the University had a very good relationship with Apotex through its owners, Dr. and Mrs. Sherman. They had been very significant benefactors, donating \$6 million over the years to the University, principally in support of research. Discussion [sic] were in progress for a very significant gift in support of the proposed new health sciences complex and the President hoped these discussions would be concluded by Christmas. All gifts had been made in compliance with and administered under University policy. These too had been disclosed to Dr. Naimark.¹

Discussions on this major Apotex donation had begun in 1991, two years before Apotex agreed to sponsor the L1 trials, as the minutes of the Governing Council Meeting of December 17, 1998 record:

In response to a member's query, the President confirmed that the University had been seeking a major donation from Apotex, the pharmaceutical company that was in dispute with Dr. Olivieri, since 1991. The University had reached agreement in principle with Apotex on the proposed gift in the spring of this year [1998].²

The size, purpose and importance of the major donation became public in a series of reports in late 1998 and in 1999. On December 9, 1998, the Naimark Report was published and in a footnote said that "Apotex has agreed in principle, to provide matching funds under the Canada Foundation for Innovation [CFI] programs in support of projects at The University of Toronto and

one or more teaching hospitals (\$20 million to the University; \$10 million to the University for affiliated hospitals).”³ The proposed Apotex donation would go principally to providing required matching funds for the CFI contribution to a “planned centre for cellular and biomolecular research that will receive \$25.6 million [from CFI] towards its \$92 million goal.”⁴ The Apotex gift would be “the largest donation to the University” and “the lead gift to its [fundraising] campaign.”⁵ The proposed centre would be “the single most important medical research project in the country.”⁶ Company Chair and Chief Executive Officer Dr. Barry Sherman told the press in September 1999 that, “the proposed \$20 million gift is part of an even more ambitious and generous philanthropic discussion he has been conducting with the university,”⁷ that could total “\$55 million.”⁸

The federal government had announced the formation of CFI in its 1997 budget. One purpose was to provide a new source of funding for Canadian universities, whose public funding base had been eroding for many years. Another was to provide an additional incentive for university-industry partnerships—a trend that federal government agencies had been encouraging. An important provision was that Universities would be eligible to apply for CFI grants only if they secured matching funds—more than half of the funding for any project had to be secured from other sources. In this instance, the proposed major donation by Apotex was intended as the foundation that, with other donations, would trigger eligibility for the announced \$25.6 million from CFI. This then, together with contributions from other sources would assemble the \$92 million financing required for the new centre.

(3) Apotex Vice-President Dr. Spino & Dr. Koren

Dr. Michael Spino had been a full-time member of the University’s Faculty of Pharmacy since 1975, but following a leave of absence spent with Apotex in 1991–1992, he joined Apotex as a full-time employee in the position of Vice-President, Scientific Affairs. From 1992 onward he has also held an appointment as professor “status only” in the University with graduate teaching duties in Pharmacy.⁹

Dr. Spino has had long associations with the Hospital for Sick Children and with Dr. Koren. In 1979, he established a laboratory at the Hospital in the Division of Clinical Pharmacology and Toxicology where he “carried out research on drug disposition, focussing mainly on patients with cystic fibrosis and asthma.”¹⁰ Following his full-time appointment with Apotex, Dr. Spino:

was allowed to retain lab and office space in the University and Hospital in order to continue his research and the supervision of graduate students and

fellows. For some years before the L1 clinical trials were initiated, Dr. Koren and Dr. Spino had collaborated on a variety of projects.¹¹

The 1993 undertaking by Apotex to acquire the development rights for the drug L1, co-sponsor a new randomized trial of L1, and supply L1 for a continuation of the existing pilot study, arose from discussions between Dr. Koren and Dr. Spino. Dr. Spino became the principal representative of Apotex during the course of the trials. The randomized trial (termed LA-01) was designed as the pivotal efficacy and safety trial for licencing purposes. This major trial was jointly sponsored by Apotex and MRC, and under the 1993 contract with the company, the Apotex funding was deposited in Dr. Koren's research accounts. Dr. Olivieri was listed as the principal investigator on the MRC application and the Council's funding was deposited in her research accounts. (See section 5A.)

It was Dr. Spino who, on behalf of Apotex, terminated both Toronto trials in May 1996 and issued the first legal warnings to Dr. Olivieri to deter her from informing patients of an unexpected risk of the drug she had identified. All subsequent written legal warnings to Dr. Olivieri, including those to deter her from publishing her findings on the drug, were signed either by Dr. Spino or by Apotex legal counsel. (See sections 5F and 5I.) Thus Dr. Spino repeatedly violated Dr. Olivieri's academic freedom. Although "The university's pre-eminent obligation is to ensure the academic freedom of all its members," and actions by Dr. Spino violating Dr. Olivieri's academic freedom were known to the University, it took no effective action to defend her right to this freedom (until January 1999). We do not know of any action taken by the University against Dr. Spino for his violations of University policy on academic freedom. (See section 5N.)

(4) Post-trial scientific collaboration between Dr. Koren & Dr. Spino

After the L1 trials were terminated, Drs. Koren and Spino continued their long-standing scientific collaboration, as summarized in a May 1998 letter from Dr. Koren to Dr. Manuel Buchwald, Director of the HSC Research Institute:

Mike is a founding member of the Division of Clinical Pharmacology/ Toxicology, which is now exactly 20 years of service at HSC. Mike's primary appointment was always in the Faculty of Pharmacy, and he was never an FTE at HSC. Over the last twenty years he has continually had a technician (Mr. Angelo Tesoro) and graduate students which he has been co-supervising with other faculty members. At the present time I co-supervise with him one Graduate student doing PhD in Pharmacy. We are interviewing a second

student now. ... Mike contributes in a major way to our Postgraduate training ...¹²

In 1998, Dr. Spino was listed as a “consultant” on the letterhead of Dr. Koren’s division in HSC. As the L1 controversy grew within HSC in the spring of 1998, Dr. Spino’s continuing use of Hospital laboratory facilities became an additional point of contention. In May, Dr. Peter Durie wrote to HSC Research Institute Director Dr. Manuel Buchwald objecting to Dr. Spino’s continuing use of HSC facilities. Dr. Durie expressed a concern regarding potential conflict of interest arising from the efforts of Apotex, and Dr. Spino in particular, to suppress adverse findings on L1 by Dr. Olivieri while funding the work of Dr. Koren who supported Apotex’s position on the drug.¹³ This concern was expressed in a petition letter Dr. Durie and many other HSC scientists sent to Dr. Buchwald a month later.¹⁴

(5) Apotex’s post-trial use of Dr. Koren’s favourable views on L1

In June 1996, although Apotex refused to reinstate the terminated trials, it agreed to continue very substantial funding for research projects supervised by Dr. Koren. This included salary support for research fellows who had been assisting with the L1 trials, which enabled them to continue employment under Dr. Koren’s supervision during the post-trial period (see section 5G(3)). This became a further element of controversy in 1997, when Dr. Koren and his Apotex-funded research fellows co-authored with an Apotex employee two conference abstracts supporting the company’s position on the drug. At the same time the company attempted through legal warnings to deter Dr. Olivieri from presenting her abstract on risks of L1 at the same conference (see sections 5I(1) and 5N(5)).

This aspect of the controversy widened in the spring of 1998 when one of these research fellows accessed a patient’s chart in the HSC thalassemia clinic without first consulting clinic staff, and Dr. Olivieri lodged a complaint with Dr. Laurence Becker, Chair of HSC’s Medical Advisory Committee. She wrote that the clinic charts contained information Apotex had been seeking to obtain, but to which it had no right.¹⁵ In response, Dr. Koren wrote to Dr. Becker regarding post-trial work on deferiprone (L1) by himself and his Apotex-funded research fellows. Dr. Koren said that it was “not correct” that “our Division* continued to play a role in the development of deferiprone for thalassemia after discontinuation” of the Toronto trials in 1996,¹⁶ adding:

*By “our Division,” Dr. Koren meant Clinical Pharmacology and Toxicology, of which he was Director between December 1992 and December 1999. Dr. Olivieri was in Hematology and Oncology, the HSC division in which thalassemia patients received their care. The Apotex-funded research fellows were appointed to Dr. Koren’s Division, but were jointly supervised by Dr. Olivieri and him during the trials.

Moreover, we have not participated in any effort by Apotex to develop the drug for thalassemia after the trial. All our efforts focus on the use of deferiprone in acute iron poisoning.^{17*}

In fact, after May 1996, with the assistance of his Apotex-funded research fellows, Dr. Koren re-analysed data from the terminated trials and was the senior author of two conference abstracts (1997—noted above), and a journal article (submitted in 1998, published in 1999), which presented findings that L1 was effective and safe for the treatment of thalassemia patients. His publications made no reference to the findings of risks of L1 published earlier by Dr. Olivieri, despite the fact that he had been fully informed of these risks. Dr. Koren did not disclose his Apotex funding support in these publications. The draft of at least one of the two 1997 abstracts was prepared by the Apotex employee who was listed as first author on both, and Dr. Koren discussed the contents of the 1999 journal article with Apotex scientific staff prior to submitting it to the journal. (See sections 5G(3), 5H(3), 5K(5), 5L(6), 5N(5) and 5R.)

The documentary record shows that, after it terminated the Toronto trials, Apotex used Dr. Koren's support for its position on the drug, including his co-authorship of publications with the company, in written submissions to the drug regulatory agency of Health Canada. In these documents, Apotex also specifically used Dr. Koren's status as a co-investigator with Dr. Olivieri on the terminated trials in its efforts to challenge her adverse findings as principal investigator.¹⁸

Dr. Spino wrote to Dr. Koren in October 1997 about Apotex's continuing "development efforts with deferiprone [L1]," noting that the company had committed "\$1,000,000" to the work on L1 in thalassemia carried out at "the Hospital for Sick Children."¹⁹ Of this total, approximately one-quarter was transferred into Dr. Koren's HSC research accounts *after* the clinical trials were terminated. Dr. Koren did not disclose that Apotex was the source of a \$250,000 grant made to him around the time the trials were terminated, when receipt of the grant is documented through the University's Department of Pediatrics.²⁰ After repeated inquiries in 1999 and 2000, the University of Toronto Faculty Association was informed by the University that Apotex was the source of the \$250,000 grant. (See section 5G(3)).

In summary, after the trials were terminated, Dr. Koren received very substantial additional research funding from Apotex and published favourable findings on Apotex's drug L1 in the treatment of thalassemia patients. The company used statements and publications by Dr. Koren in communications with Health Canada. Dr. Koren did not disclose that Apotex was the source of

*Dr. Koren's study of the efficacy of L1 in acute iron poisoning was conducted in an animal model and was funded by Apotex. (Naimark Report, pp. 142–3.)

a \$250,000 grant he received around the time the trials were terminated, and the University did not require him to do so in a public listing of grants received by members of his division in the Department of Pediatrics. Dr. Koren did not disclose his Apotex sponsorship in the publications noted above, and in this respect and others he failed to act in accordance with widely accepted standards of conduct for publication in biomedical fields (see section 5R). We do not know of any action taken by the University against Dr. Koren for his conduct in these publications.

(6) HSC & donation discussions

It has been reported that during the period 1993–1998, Apotex provided support for research projects at HSC totalling \$1,337,539,²¹ which may include the \$1,000,000 for development work on L1 in thalassemia during and after the LA-01 and LA-03 trials. In June 1998, after agreement in principle on the major donation (\$20,000,000 for the University and \$10,000,000 for the teaching hospitals) had been reached between the University and Apotex, the University approached the foundations of its affiliated hospitals to explore their interest in participating. By this time, HSC officials had been informed that media coverage of the controversy could be expected once an article on the risks of L1 by Dr. Olivieri, then in press, was published in the *New England Journal of Medicine*.²² Upon learning that Apotex was the source of the major donation in question, members of the HSC Executive and of the Board of the HSC Foundation decided against participation, citing the L1 controversy as a reason.²³ (See sections 5L(1) and 5L(7).)

(7) Donation discussions suspended

After extensive media coverage of the L1 controversy began in mid-August 1998, the parties to the agreement in principle decided to delay proceeding to a formal agreement on the major donation. The minutes of the University's Governing Council for December 17, 1998 summarized the reasons given in a discussion between President Prichard and a Council member:

This fall the University and Apotex had agreed that discussions to finalize the gift should be suspended until the matters in dispute were resolved. The member who had raised the question noted that she supported this course of action. There was real concern that Apotex should be cleared of wrongdoing in this matter before discussions concerning a donation to the University resumed. The President indicated that Apotex shared this view and that the decision to suspend the discussions had been mutual.²⁴

Thus, two pre-conditions for lifting the suspension on discussions were stated:

- (i) resolution of “the matters in dispute;” and

(ii) “Apotex should be cleared of wrongdoing.”

(8) Donation discussions resumed

The manner and extent to which the University considered these two pre-conditions to have been satisfied by 1999 are unclear, but it is clear from media coverage and minutes of University governing bodies that the mutual suspension on discussions on the major donation had been lifted prior to September 1999.²⁵ Apotex introduced an additional consideration: it asked the University to assist it by writing to the federal government about proposed changes to drug patent regulations it considered adverse to its interests as a manufacturer of generic drugs.²⁶ President Prichard agreed to assist and wrote to the Rt. Hon. Jean Chrétien, Prime Minister, and four other federal ministers on behalf of Apotex. The *Toronto Star* obtained a copy of the President’s letter and published excerpts on September 4, 1999. The *Star* reported:

Prichard told Chrétien and the others, in a letter obtained by the *Star*, that Apotex Inc. chairman Sherman has promised “a very substantial philanthropic commitment” to the university. He went on to say that Apotex “has advised us that the adverse effect of the new regulations would make it impossible for Apotex to make its commitment to us.” Prichard urged the Prime Minister and Liberal cabinet members to do what is necessary “to avoid the serious negative consequences to our very important medical sciences initiative.”²⁷

Following the coverage in the newspaper, President Prichard’s action was discussed in a meeting of the University’s Executive Committee on September 7, 1999. The minutes recorded:

The President recalled a *Toronto Star* business story the previous Saturday reporting on a letter he had written to the federal government requesting that Ottawa allow an extension of 30 days in its review of drug patent protection regulations. The President explained that the letter had been written following a request for assistance from Dr. Barry Sherman, President, Apotex Inc and the Apotex Foundation, because the proposed new legislation might make it financially impossible for Apotex to fulfill its \$20 million donation towards the University’s Centre for Cellular and Molecular Biology Research. This was a project for which major funding had been secured from the Canada Foundation for Innovation and was anticipated from the Ontario Innovation Trust.²⁸

It appears from these statements that, without the \$20 million from Apotex, the additional matching funds required for the \$92 million building, including the \$25.6 million from the newly created federal government agency CFI, could be in jeopardy.²⁹

President Prichard apologized to the Executive Committee for his action. He acknowledged he had made “a mistake” and that his letter had:

placed the University in an inappropriate position of intervening in a matter beyond the legitimate scope of the University's jurisdiction.³⁰

On September 16, 1999 the President told the University's Governing Council that:

While his intervention had been procedural and not substantive, he still believed it to be wrong.³¹

The lobbying efforts with the Government of Canada were unsuccessful and in early November 1999 Apotex announced that its proposed \$20 million donation would be reduced to \$1 million.³² A year later, the University announced that Apotex had made a donation in the \$5 to \$10 million range.³³

5

*Review & Analysis
of Events*

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5A | The Toronto L1 trials (LA-01 and LA-03)

(1) Origins of the trials and early positive findings

THALASSEMIA MAJOR PATIENTS, because they are dependent on regular blood transfusions, are subject to chronic toxicity from iron loading resulting from this treatment. The excess iron affects major organs such as the heart, liver and endocrine glands. If untreated, over a period of years this results in morbidity and mortality (usually from cardiac arrest). Unfortunately, the standard treatment for iron loading—subcutaneous infusion of the iron-chelation drug deferoxamine (DFO)—is onerous, and non-compliance is therefore a major concern, especially among adolescents and young adults. The development of a safe and effective iron chelator that could be taken orally would be of great value to many thousands of people worldwide. It was hoped that deferiprone (L1), one of a family of chemically similar iron chelators that was synthesized in England in the early 1980s, might serve this purpose.

Clinical studies of L1 in England with small numbers of patients were promising. As a result, Dr. Nancy Olivieri, a specialist in hematology and internal medicine at the Hospital for Sick Children (HSC) in Toronto decided to organize a trial in her clinic, which served the largest group of thalassemia patients of any centre in North America. L1 was not commercially available, but Dr. Robert McClelland in the Chemistry Department of the University of Toronto agreed to synthesize sufficient quantities for the trial.

In the summer of 1988, Dr. Olivieri obtained regulatory approval from the Health Protection Branch (HPB) of Health Canada for an experimental trial of L1, and ethical approval from the Human Subjects Review Committee (later called the Research Ethics Board—REB) of HSC. The planned trial cohort was to consist of patients unwilling or unable to accept the standard therapy. She then applied to the Medical Research Council (MRC) in September 1988 for funding for a two year “Pilot Study,” for which she was principal investigator.¹ Dr. Gideon Koren was included in the application as a co-investigator. Later phases of the planned study were to include pharmacokinetic analysis, his area of expertise.² The initial funding application was successful, and the investigators later received two additional one-year grants (the last being a “terminal” grant) so that MRC funded the pilot study for a four-year period 1989–1993.³ The pilot study was titled, “Evaluation of Efficacy of the Oral Iron Chelator L1 in removal of Hepatic Iron in β -Thalassemia Patients”⁴ on a 1990 REB protocol-approval form, and this title was retained in REB records thereafter.

The pilot study included several efficacy and safety tests. The initial assessment phase emphasized short-term measures of efficacy, such as

excretion of excess iron. These would help determine which patients could safely be enrolled in a second, longer-term phase of the study. The primary measure of efficacy for the long-term study was hepatic iron concentration (HIC), the most accurate measure of tissue iron burden. The initial objective was a substantial reduction in HIC after one year of treatment, followed by further reduction and maintenance of HIC in a safe range in the longer term. HIC also is an important safety indicator: if iron-chelation treatment is ineffective, patients become subject to the chronic toxicity of iron loading. Determination of HIC required chemical analysis of tissue samples obtained by percutaneous liver biopsy (performed with patients' consent).⁵ Patient enrolment in the long-term phase of the study began in the second half of 1990.⁶ Enrolment conditions for the long-term phase included baseline measurement of HIC by biopsy. The biopsy procedure and its purpose were explained to trial subjects in the information and consent forms.⁷

Results from the first two years of the pilot study proved encouraging to Dr. Olivieri and others in the scientific community. She and several American investigators met with Dr. Steven Fredd and other staff of the United States' Federal Drug Administration (FDA) in 1991 and again in 1993 to discuss development of the drug for therapeutic use.⁸ Dr. Fredd advised that three studies should be performed for FDA licencing approval: first, a continuation of the pilot study in Toronto as a long-term efficacy and safety trial; second, a randomized trial to compare the efficacy and safety of L1 to the standard therapy, DFO; and third, a short-term safety trial with a large number of patients to assess acute toxicity effects of L1 (severe loss of white blood cells and joint damage), which had been observed in a few individuals in studies elsewhere. He advised also that a pharmaceutical manufacturer should be involved in any licencing effort.⁹

Among the investigators present in the meetings with FDA was Dr. Gary Brittenham, a hematologist at Case Western Reserve University. In the fall of 1992, Dr. Olivieri began to collaborate with Dr. Brittenham on iron-chelation research, and he agreed to perform HIC determinations for her patients. A decade earlier, he had developed the only accurate non-invasive method for HIC determination: magnetic susceptometry with a specially constructed apparatus containing a superconducting quantum interference device (SQUID). Because his laboratory in Cleveland was the only site in North America with the equipment to perform this measurement, patients were obliged to travel there for the test.¹⁰

Dr. Olivieri designed a randomized, comparison trial and, again with Dr. Koren as co-investigator, applied to MRC in October 1991 for funding. This larger, more elaborate trial required approximately double the annual funding for the pilot study. The application was not successful—MRC declined to

sponsor, on its own, a new randomized trial of L1 and instead awarded a one-year “terminal grant” for 1992–1993 for the existing pilot study.¹¹ However, a response from MRC in 1992 suggested re-application under the university-industry program.¹² This would involve securing an industrial co-sponsor. Dr. Koren approached Apotex Inc. through his long-time pharmacology colleague in the University of Toronto and HSC, Dr. Michael Spino, who had recently become a full-time Apotex employee. Apotex was a large and successful manufacturer of generic drugs, but had become interested in developing its own drugs through clinical trials. Both Dr. Olivieri and Dr. Koren had experience in clinical trials that would be useful to Apotex. Also, the structure of L1 and a method of synthesis were well known, and the owners of the commercial rights to use L1 in the medical treatment of iron overload (the British Technology Group) agreed to transfer the rights to Apotex. In early 1993, Apotex agreed become the industrial sponsor of L1 trials with the intention of eventually seeking regulatory approval to market the drug. An internal Apotex memo reported that the arrangement between the company and Drs. Olivieri and Koren was “a good one because the investigators secured the support of a pharmaceutical company to ensure development and Regulatory approval and the company was able to save the time and expense of preclinical development.”¹³

L1 is relatively inexpensive to produce. The number of thalassemia patients in North America is relatively small, but large potential markets for an inexpensive iron chelator exist in the Mediterranean region, the Middle East and southern Asia where the great majority of persons with this disease reside, and where the high cost of DFO treatment limits its availability. As well, if the drug proved sufficiently effective and safe in trials with thalassemia patients to be licenced as an iron chelator, it might potentially be used to treat other diseases of iron metabolism more common in North America, notably hereditary hemochromatosis.*

(2) The contracts and research teams

*Hereditary hemochromatosis is a disease that results in iron loading of organ tissues. In persons with this disease, the clinical manifestations of chronic iron toxicity can be prevented by early diagnosis and treatment, either by regular phlebotomy or by an iron-chelation drug. Its frequency of occurrence is much higher than that of thalassemia in the North American population. About one in ten Caucasians carry the gene, which is autosomal recessively inherited. The observed disease frequency is approximately 1 in 300 adults. By contrast, a 1993 survey indicated that there are fewer than 1000 persons with thalassemia major in all of Canada and the United States (see A. Cohen *et al.*, *Cooley's Anemia*, NIH report, 1995, pp. 7–8).

Apotex undertook to co-sponsor with MRC the new randomized comparison trial, designed as the pivotal, “Phase III” efficacy and safety trial for licencing.¹⁴ This was later referred to as the LA-01 trial.

Clinical trials often require a range of medical expertise and may involve scientific collaborators who are not formally considered “investigators” in a trial, but nevertheless are part of an ongoing research group. The 1993 application to MRC for co-sponsorship of LA-01 noted the research group on iron chelation formed by Dr. Olivieri, which had been engaged in studies on both L1 and the standard drug DFO for several years. Clinical trials also require support staff. The budgets approved by Apotex and by MRC included funds to cover salary costs of scientific and technical support staff, and to cover specialized monitoring tests not considered part of standard medical care of patients.

In return for access to data, Apotex also agreed to supply L1 free of charge for the continuation of the already existing pilot study as a separate, long-term trial. This trial was henceforth called LA-03.

Dr. Olivieri’s Iron Chelation Research Group. A 1996 listing of group members associated with the LA-01 trial included eight medical scientists, three postdoctoral research fellows, several nursing staff, a laboratory technician, a secretarial assistant, several data managers and several summer student assistants. The list of scientists included Dr. Olivieri (“Supervisor”), Dr. Koren (“Pharmacology supervisor”), Dr. Brittenham (“liver biopsy SQUID”), Dr. Peter Liu (“MRI and MUGA interpretations”), Dr. Laurence Blendis and Dr. Peter Chait (“liver biopsies”), and Dr. Ross Cameron (“Interpretation and analysis of liver biopsies”) the pathologist who provided expertise in liver histology.¹⁵ Some of those listed for LA-01 also worked on the LA-03 trial. In addition to the scientists included in the 1996 list, Dr. Olivieri had collaborated with other scientists on various aspects of the Toronto trials, for instance Dr. Robert Jacob of the United States Department of Agriculture (plasma vitamin C concentrations).¹⁶ None of the scientists received salary support from Apotex funds, but some others in the group, including research fellows, received Apotex salary support.¹⁷

Dr. Olivieri’s scientific and clinical role as principal investigator for the two trials. Dr. Olivieri is a specialist in hematology and internal medicine, the two disciplines most central to the work of these trials. From her work in the 1980s, she was already an acknowledged expert in the treatment of thalassemia and she was the treating physician of patients in the two trials. She was also the investigator having a substantially greater weekly allocation of her time to the L1 trials than the other scientists. The scientific

protocols for the LA-01 and LA-03 trials, as well as for the original pilot study, were principally designed by her.

Dr. Koren's administrative role in negotiation of the arrangements with Apotex in 1993. Then Associate Director for Clinical Research in the Hospital's Research Institute, Dr. Koren had considerably more administrative experience than Dr. Olivieri. He had served as Chair of the REB until December 1992, when he was appointed Director of the Division of Clinical Pharmacology and Toxicology. For these reasons, in addition to his long-time acquaintance with Dr. Spino, he played a leading role in both the negotiations with Apotex and in processing the LA-01 trial protocol through the REB. "As promised, I will take care of the contact [sic] and report with Research Ethics Committee of our hospital," he wrote to an Apotex official in a letter setting out a budget for the LA-01 trial, a month before the contract for it was signed.¹⁸

Joint Apotex-MRC sponsorship of the randomized trial (LA-01). Dr. Olivieri and Dr. Koren signed the formal contract with Apotex on April 23, 1993.¹⁹ This contract was for three years from the date of signing. In it, Apotex agreed to fund the randomized trial at \$128,000/year for "research costs" (including salary support for two postdoctoral research fellows), and also to cover several other specified costs. The protocol for this study had been approved by the REB of HSC in December 1992.²⁰

In May, Drs. Olivieri and Koren applied to MRC for funding for this trial, titled "Randomized Trial of Subcutaneous Deferoxamine and Oral L1 in Iron Overload," under the university-industry program. The application was for three years of funding, October 1, 1993—September 30, 1996, and named the University of Toronto as "the University" and an Apotex subsidiary, Rh Pharmaceuticals Inc., as "the Company."²¹ The application to MRC listed the Apotex contribution as the same \$128,000/year specified in the April 1993 contract. It gave a detailed description of the planned trial, including a budget for a cohort size of sixty-six patients. The application was endorsed by Dr. Robert Haslam, HSC Pediatrician-in-Chief and Chair of the University's Department of Pediatrics, and by Mr. George Chiasson, Associate Director for Administration in the HSC Research Institute, as required on the standard MRC form. The application was successful, for the requested \$101,028/year.²² Although the April 1993 contract did not use the term, this randomized trial

was the one subsequently referred to as LA-01, and the April 1993 contract pertained to the LA-01 trial.*

Although Dr. Olivieri was the principal investigator on the MRC application and the treating physician of patients who were enrolled, the Apotex funds for the LA-01 trial went into HSC research accounts that were under Dr. Koren's control.²³ He also "maintained the records" of accounts of the Apotex funding for the LA-01 trial, as well as for the LA-03 trial throughout the period of Apotex sponsorship.²⁴ The MRC funds went into HSC research accounts under Dr. Olivieri's control. The MRC application made provision for salary support for a third research fellow. Dr. Olivieri reported to us that Dr. Koren had the lead in recruiting the research fellows, although they were co-supervised by her and him when working on the trials.

There was initially no formal contract as such for the LA-03 trial, the new term for the continuation of the pilot study that had been sponsored by MRC during 1989–1993 (sometimes also called the "compassionate use" trial because the patients enrolled in it were unwilling or unable to comply with the standard therapy). An informal arrangement was recorded in Dr. Koren's letter to Apotex of March 22, 1993, although most of that letter dealt with the proposed LA-01 trial. Dr. Koren wrote that Apotex had agreed to supply L1 free of charge for patients in the LA-03 trial "for the same 3 years [as for LA-01]" in return for which, "all data on efficacy, or safety generated on these patients can be used by the sponsor for regulatory submissions."²⁵ Other than supplying the drug at no charge, Apotex did not undertake to provide funding expressly for LA-03 at this stage.²⁶

Dr. Brittenham's scientific role in the Toronto trials. The LA-01 trial protocol specified HIC determinations would be obtained primarily by SQUID (as an alternative to biopsy) and thus, necessarily, in Dr. Brittenham's laboratory in Cleveland. Later (July and October 1995) protocol modifications that were approved by the HSC REB and by Apotex specified that Dr.

*These details are important for several reasons. (i) The L1 controversy erupted when Apotex terminated both the LA-01 and LA-03 trials in May 1996. Dr. Aileen Moore, the REB Chair during 1996–1999 later stated incorrectly that only the LA-01 trial was terminated in May 1996, and that the LA-03 trial "continued" as an MRC-sponsored study. In fact, MRC sponsorship for the pilot study (that continued as LA-03) ended in 1993, and the trial MRC co-sponsored during 1993–1996 was, quite specifically, the randomized trial (LA-01). (ii) The Naimark Review incorrectly concluded that the LA-01 contract also governed the LA-03 trial, perhaps because it was not given access to the contract later signed for LA-03. In fact, there was no formal agreement between the investigators and Apotex for the LA-03 trial (other than a paragraph in a 1993 letter by Dr. Koren) until a contract for it was executed in October 1995. (iii) The Naimark Report incorrectly stated that, "the University [of Toronto] was not involved in the processes involved in the establishment, conduct or financing of the [L1] trials." In fact, the University had ongoing involvement with the trials, as well as the subsequent controversy. (See also sections 5G, 5M, 5N, 5O.)

Brittenham would be responsible for all assay of HIC (whether biopsy or SQUID), “to ensure uniformity of assessment.”²⁷ The Apotex contract provided for funds to reimburse patients “for the cost of flights from Toronto to Cleveland.” However, Dr. Brittenham was not a signatory either to the contract or to the protocol for LA-01, and the contract provided no funding for the use of his laboratory facilities. He was responsible as well for liver iron assay for the LA-03 trial but Apotex had no contract with him and provided his laboratory with no funding for this trial. In both cases, Dr. Brittenham was simply continuing his scientific collaboration with Dr. Olivieri, begun prior to the involvement of Apotex in L1 development, as both of them reported to us.

Monitoring tests for safety and efficacy. The LA-01 contract with Apotex and the application to MRC for co-sponsorship specified certain safety and efficacy tests “not part of routine patient care and not covered by the [Ontario provincial] health insurance” to be covered by Apotex or MRC funds.²⁸ These included magnetic resonance imaging (MRI) of the heart, liver and pituitary gland, and hormonal tests. Liver biopsy, specified in the protocol for histology as well as HIC, and discussed in the MRC application, was not among the listed “research” tests, since by 1993 annual liver biopsy had become a part of routine management of patient care for patients with thalassemia major in the Hospital for Sick Children.

The objective and the principal measure of efficacy for the LA-01 trial. The trial protocol stated that the objective was to compare L1 with the standard therapy DFO as to: efficacy, safety, compliance of subjects with treatment, and quality of life during treatment. As with the pilot study (later termed LA-03), the “principal efficacy measure” for this trial was reduction of tissue iron stores as determined through HIC. This was to be measured

in pre-trial assessment [for baseline], at the interim assessment after one year of therapy and at the final assessment after two years of therapy.

The protocol specified that the principal efficacy criterion was an “endpoint” criterion and that if the final HIC

of patients treated with L1 is within 20% of that of patients of with DFO, then the two treatments will be considered equally effective.

The statistical procedure for this determination was specified.

The LA-01 protocol specified that “SQUID will be used as the principal measure of liver iron [HIC],” but because “liver biopsies, but not SQUID, allow assessment of the histopathology of the liver,” it also specified that:

Each patient will undergo percutaneous liver biopsy at the site where they are randomized [enrolled]

and that annually thereafter:

When possible (i.e., when patients consented), liver biopsies will also be obtained from the patients to provide both supportive measurement of liver iron content [HIC] and the histology which is important for the proper clinical management of the patients.^{29*}

The LA-03 contract. A formal contract for the LA-03 trial was not signed until October 1995. This contract came about for two reasons. First, both Apotex and the investigators had come to appreciate that this trial was inadequately funded. Without additional support staff the investigators were unable to supply the quantities of organized data Apotex had been requesting. The October 1995 contract provided Apotex funding for LA-03, for two years, 1995–1997, at the rate of \$58,274/year (with an additional \$27,500 in the second year, to come from a foundation grant, or from Apotex in the event of an unsuccessful application to the foundation). Some of the new funding was for salary support for a data manager. Second, in 1995 the investigators became concerned over data indicating that L1 was not sustaining its efficacy in some patients in the long-term (LA-03) cohort. The contract made provision for possible additional funds:

Any patients confirmed to be inadequate responders to L1 will be removed from the LA-03 trial. These patients will be enrolled in a separate study to determine if a reason for the inadequate response can be identified. For those patients where there is mutual agreement that the response to L1 is inadequate,** Apotex will provide a budget of \$5,000 for the total investigation to determine if a reason for the inadequate response [of some patients to the drug] can be identified.³⁰

*The details on liver biopsy for determination of hepatic iron concentration (HIC) and histology (for both LA-01 and LA-03) are central to the subsequent L1 controversy for several reasons. (i) Dr. Olivieri's Toronto trials were the only clinical trials of L1 anywhere in the world that included baseline HIC and liver histology. It was through HIC determinations that she identified the risk of loss of sustained efficacy of the drug in 1996, and through review of histology in the charts that she identified the risk of progression of liver fibrosis in 1997. Apotex tried to suppress information on these risks through legal warnings to her. (ii) In 1998 Apotex sought marketing licences for L1 primarily on the basis of another trial (LA-02) that did not include baseline HIC or histology. (iii) After Dr. Olivieri identified the two risks, Apotex attempted to discredit the use of liver biopsy as a diagnostic procedure in treatment of thalassemia in both trial and non-trial settings. (iv) In 1999 Dr. Koren and Dr. Hugh O'Brodovich, HSC's Pediatrician-in-Chief, made incorrect allegations against Dr. Olivieri's use of liver biopsy—allegations contrary to practice established in the medical literature, but similar to statements against the use of liver biopsy made earlier by Apotex. These allegations were not disclosed to Dr. Olivieri until after action was taken on the basis of them. (See sections 5E, 5F, 5I, 5K, 5P, 5Q and 5U.)

**Between March 1995 and October 1995, when the LA-03 contract was executed, Dr. Olivieri had withdrawn seven patients from the LA-03 trial because of significant loss of sustained efficacy of the drug in their individual cases (see section 5D). However, it appears from the wording of the contract quoted here that Apotex still did not agree that there was significant loss of sustained efficacy in any patients.

(3) Confidentiality provisions in the LA-01 contract

The contract for the LA-01 trial signed by Drs. Olivieri and Koren with Apotex on April 23, 1993 contained the following clause giving Apotex control over communication of findings during the life of the contract and for one year following its termination:

7. Confidential

All information, whether written or not, obtained or generated by the investigators during the term of this agreement and for a period of one year thereafter, shall be and remain secret and confidential and shall not be disclosed in any manner whatsoever to any third party, except to an appropriate regulatory agency for the purpose of obtaining regulatory approval for manufacture, use or sell L1 [sic] unless the information has been previously disclosed to the public with the consent of Apotex. The investigators shall not submit any information for publication without the prior written approval of Apotex.³¹

In contrast, the protocol for this trial did not contain this restriction. The protocol and later modifications to it were approved by the REB, and signed by Drs. Koren and Olivieri as investigators, and Dr. Spino and other Apotex staff. Aside from the standard legal requirements concerning confidentiality of patient records, the LA-01 protocol contained only the following clauses on communication of findings:

All information provided to the investigator by the sponsor is to be considered confidential unless otherwise stated.

The investigators are encouraged to publish the results of this study in the medical literature. All publications and abstracts are to be reviewed by the sponsor prior to submission. The sponsor will provide the investigators with financial assistance in the cost of publication.³²

Thus, the protocol did *not* materially restrict communication by the investigators of their findings from the study. It gave the sponsor the opportunity to review, but not prevent, publications.

Another provision of the protocol, Clause 10.0, required that adverse reactions be reported to the REB, and also the federal regulators (a legal requirement). Since Clause 7 of the contract gave Apotex the right to refuse communication of any information during its term and for one year thereafter, the contract was potentially in conflict with both the protocol and drug regulations.

This was not the only significant difference between the two documents. The trial protocol specified Dr. Brittenham as the scientist responsible for the primary endpoints (HICs) required for determination of efficacy and safety, as well as for submissions to regulatory authorities, but he was not a party to the trial contract. Both these discrepancies contributed to the subsequent

controversy, although the confidentiality conflict surfaced first and is more widely known.

The LA-01 protocol and all subsequent modifications were formally approved by the REB, but the contract was formally approved neither by the HSC administration nor the University. Dr. Olivieri was widely criticized for signing a contract with a one-year, post-termination publication ban without first having it reviewed. She herself later stated publicly that it was a “very, very naïve mistake” to have signed a contract with such communication restrictions.³³ After the L1 controversy became public in 1998, it was implied that, had the contract been reviewed in advance, the administration of either the Hospital or the University would not have approved the contract and might have “counsel[led] the investigators against incurring inappropriate obligations.”³⁴ To assess whether this was likely to have been the case, and the extent to which it is reasonable to fault Dr. Olivieri, it is necessary to review the policy and practice of the time.

In fact, the confidentiality provision of the contract violated no existing publication policy in regard to sponsored research. In particular, the University of Toronto Publication Policy (in force since 1975), expressly permitted a “12-month” post-termination publication ban in cases “where the sponsor has industrial or commercial rights which it wishes to protect.”³⁵ Drs. Koren and Spino, who negotiated and approved the contract along with Dr. Olivieri, had considerable experience in research in the University, so it is likely they understood that the contract complied with existing University policy. At the Hospital:

[T]here was no policy that clearly required review and approval of contracts in advance. Some investigators did submit proposals for approval but apparently many did not.³⁶

Furthermore, we have seen no policy in effect at HSC governing confidentiality clauses that would have provided a basis for any HSC administrator to have refused to approve the contract. Indeed, after the 1993 LA-01 contract was signed, the Hospital administration formally approved a contract between another investigator and another drug company with similarly restrictive provisions.³⁷ It is of note that on March 26, 2001, the University announced that it and its affiliated teaching hospitals were now changing their policies so as to prohibit contract clauses that could be used to prevent a clinical investigator from disclosing risks, and the Dean of Medicine was cited in the press as having said that, “the whole Olivieri-Apotex conflict would likely have been avoided,” had the new policy been in place at the time the LA-01 contract was signed.³⁸ Therefore it is reasonable to conclude that, had the LA-01 contract been submitted to either the University of HSC for review in 1993, it would have been approved.

We do not know why there were significant discrepancies between corresponding provisions in the contract and the protocol (both in regard to confidentiality and in regard to the significant role of Dr. Brittenham in the trials). We do know that, by his own written account, Dr. Koren undertook to “take care of” both documents.³⁹ It was obvious from the protocol document submitted to the REB that the LA-01 trial had a commercial sponsor, and this was made clear on the application to MRC for funding under the university-industry program. Both the members of the REB who approved the protocol, and the University and Hospital administrative officers who endorsed the MRC application had ample opportunities to ask to see the contract. Although the contract had already been signed, the University or the Hospital could have refused to endorse the MRC application and thus held up the project pending review of the contract. They did not do so. Perhaps, like Dr. Olivieri, they relied on Dr. Koren’s experience and judgment in these matters, since he had just completed a term as REB Chair and was currently in a relevant administrative capacity, Associate Director for Clinical Research. These discrepancies between the contract and the protocol are a reflection of the Hospital’s “weak policy infrastructure.”⁴⁰ It was an uncontroversial finding of the Naimark Review that:

At the time the Trials Contract was executed (1993) the requirement for detailed a priori institutional review of contracts with external sponsors, if there was one, was articulated so imprecisely and, we were told, was so frequently ignored as to be, for all practical purposes, non-existent.⁴¹

Conclusions

1 | Drs. Koren and Olivieri should not have signed the LA-01 contract with the confidentiality clause that it contained: in agreeing to such a restrictive clause they potentially constrained their ability to meet their ethical, legal and administrative obligations, and also potentially restricted their academic freedom. However, it must be noted that by signing the contract they breached no HSC or University policy on contract research, and likely did exactly what other researchers also did at the time. Further, had the contract been reviewed by either the Hospital or the University, it is probable that it would have been approved as it was in compliance with the University’s Publication Policy.

2 | The Hospital for Sick Children and the University of Toronto should have had, and should have enforced clear policies that required review of all contracts. These policies should have prohibited confidentiality clauses that could be used in efforts to prevent researchers from exercising their right to communicate findings of risk in clinical trials. It is paramount that investi-

gators be unimpeded in meeting their obligation to inform participants of any new information that might affect their willingness to continue in the trial.

3 | The Medical Research Council must also accept a share of the responsibility. Its university-industry grants program should have incorporated measures to ensure that contracts between investigators and industrial sponsors under this program did not contain provisions in conflict with MRC’s own guidelines for ethical conduct of research.

4 | The University of Toronto announced on March 26, 2001 that it and its affiliated teaching hospitals were instituting a new publication policy that would prohibit inappropriate communication restrictions in clinical research contracts. This means that the University has now recognized that its previous policy, the one in force when Drs. Koren and Olivieri signed the LA-01 contract with Apotex, was not appropriate for clinical research.

5 | There is an ongoing broad basis for concern about policy and practice in this area. We have been provided with examples of contract clauses more restrictive than the one Dr. Olivieri and Dr. Koren signed in 1993. These were proposed in recent months by several major drug companies to researchers elsewhere in Canada and the United States, and were actually approved by institutional research administrators and signed by the researchers (see section 3A). Concerted support by all universities, their affiliated teaching hospitals, and government granting councils for a national policy will be required to bring about appropriate and uniform standards, and mechanisms to ensure enforcement of standards, to protect the interests of research subjects across Canada.

(4) Absence of confidentiality provisions in the LA-03 contract

Apotex issued a contract for the LA-03 trial to Dr. Koren and Dr. Olivieri on October 2, 1995 and they signed it on October 10 and 12, respectively. Unlike the LA-01 contract, the LA-03 contract contained no “confidentiality” provision of any kind, post-termination or otherwise. Nor did this contract make provision for Apotex ownership of data. It stated that Apotex would be provided data and could use it:

Funding for LA-03 will be provided to enable adequate support staff to maintain records and to provide Apotex with the information they require for Regulatory purposes. ... It is understood that maintenance of the funds is contingent upon provision of information to Apotex for data outlined in the revised LA-03 protocol.

The protocol specified the types of data and recording methods, and provided that:

All publications and abstracts must be reviewed by the sponsor prior to submission,

but did not provide the sponsor with any right to prevent communication. The October 1995 contract also stated:

this agreement *supplants* any other previous agreement on this [LA-03] cohort of patients.⁴² (emphasis added)

This contract was signed *after* both the LA-01 contract (April 23, 1993) and the LA-02 consulting contract (June 17, 1995) discussed below. Thus any possible argument that data from the LA-03 trial was restricted by wording in the LA-01 contract (or the LA-02 consulting contract) is nullified by the express wording of the LA-03 contract.

The two unexpected risks of L1 were identified (in 1996 and 1997) in data on patients in the long-term trial cohort, LA-03. The controversy began in May 1996 when Apotex terminated both Toronto trials and issued legal warnings in an effort to deter Dr. Olivieri from informing patients and others of the first of these risks. It is a remarkable feature of the L1 controversy that *Apotex had in fact no contractual basis for legal warnings in regard to LA-03 data*. Ironically, this fact played no role in the developing controversy.

(5) Termination provisions in the protocols and contracts

Section 7.0 of the protocol for the LA-01 trial, entitled, "Trial Discontinuation," contained the provision:

The trial can be discontinued because of a decision by the monitoring board, principal investigators or sponsor.⁴³

Subsection 8.3 of the protocol for the LA-03 trial, entitled "Early termination of the trial" contained the provision:

The protocol may be terminated because of concerns of long term efficacy and safety of deferiprone. ... In the event of termination *for a reason other than safety*, the investigator will provide documentation on the appropriate forms provided and carry out the necessary assessments for termination of the study.⁴⁴ (emphasis added)

This subsection did not specify which persons or agents could terminate the trial, but from a reading of the entire protocol the only reasonable inference is that the intent was the same specified in the LA-01 protocol.

The LA-01 contract had a termination clause that gave any party the right to terminate:

in the event that there is a breach of any term or condition of the Agreement [contract].⁴⁵

The LA-03 contract expressly acknowledged the right of Apotex to terminate the trial unilaterally:

These funds will continue to be provided by Apotex until licencing of L1 or *the decision by Apotex to terminate the LA-03 study* or the development of L1.⁴⁶ (emphasis added)

Apotex exercised its right under the contracts, as well as under the protocols, and *terminated both trials* (and protocols) on May 24, 1996. This is one of the most fundamental facts in the entire L1 controversy. (See sections 5F, 5K, 5O and 5P.)

It is also of note that neither protocol contained any provision covering the interests of trial participants in the event that the sponsor abruptly terminated the trial without advance notice. When this occurred, the Dean of Medicine, Dr. Arnold Aberman was asked to intervene to mediate a new arrangement on an *ad hoc* basis.

Conclusions

1 | Data generated in the long-term (LA-03) trial was *not* subject to a confidentiality clause (unlike data generated in the LA-01 trial that was governed by a separate contract).

2 | Apotex had the contractual right to terminate *both* the LA-03 and LA-01 trials, unilaterally (a right it exercised on May 24, 1996).

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5B | Designing the international trial (LA-02)

(1) The consulting contracts

IN MEETINGS INVOLVING Dr. Olivieri, Dr. Brittenham and others, the FDA had stated that it required performance of three trials before it would consider granting a marketing licence for L1. The third trial, termed LA-02, was a short-term (one-year) acute toxicity trial, to assess known adverse effects of L1. Since these effects had been observed only in small numbers of patients world-wide, this trial required enrolment of a large cohort. For this reason, the main trial sites were to be located outside North America, where the rates of occurrence of thalassemia are higher. This trial was announced in Dr. Olivieri's April 1995 article in the *New England Journal of Medicine*, with a brief summary of its purpose and an acknowledgment of Apotex sponsorship.¹ In a letter to Dr. Olivieri in February 1996, Dr. Spino of Apotex noted the limited purpose and duration of this trial,

... the LA-02 trial... is a safety study of shorter duration (1 year).²

Although Apotex agreed to fund this trial, it did not have either the expertise to mount it, or the contacts in the international medical community to organize sites. Drs. Olivieri and Brittenham had both the expertise and the contacts, and they agreed to work with Apotex to organize this trial. Apotex's dependence on them for both expertise and contacts is clear from internal Apotex correspondence.³ It was originally intended that Drs. Olivieri and Brittenham would be investigators, along with the site investigators, but under FDA regulations only treating physicians of patients in a trial can be considered as investigators. It was agreed therefore that Drs. Brittenham and Olivieri would act as consultants to the trial under personal services contracts with Apotex.

Apotex engaged Drs. Olivieri and Brittenham to design the LA-02 protocol, to organize sites to implement it, and to assist in overseeing the trial. Their consulting contracts had a two-year duration and provided for an annual fee of \$30,000 USD, and reimbursement for expenses. Dr. Olivieri's contract was signed June 17, 1995, but was retroactive to October 1, 1994, because detailed planning for this trial had begun in 1994.⁴ The three main sites for the trials were in Italy, but there also was a small site in Philadelphia. Performance of these contracts involved considerable time, travel and effort, as well as expertise. For example, Drs. Olivieri and Brittenham engaged the investigators at the trial sites and trained them, and supervised enrolment of patients. They also were leading members of the trial's Steering Committee, which Dr. Olivieri chaired. There was no comparable contract with Dr. Koren for this trial, since he had neither the relevant medical expertise, nor the relevant medical contacts required by Apotex for this purpose.

The LA-02 consulting contracts had a three-year post-termination publication ban, expressed in the following terms:

6. Publication

“Apotex” encourages publication of the results of studies in peer reviewed journals. However, none of the material generated from “Apotex” sponsored studies may be submitted for presentation or publication without the prior written consent of “Apotex”. Such consent will not be unreasonably withheld and will be freely granted when patent and other commercial considerations, if any, do not preclude such public dissemination of this information.

7. Confidentiality

All information, whether written or not, obtained or generated by “The Consultant” during the term of this contract and for a period of three (3) years thereafter, shall be and remain secret and confidential and shall not be disclosed in any manner, whatsoever to any third party, except to an appropriate regulatory agency for the purpose of obtaining regulatory approval for manufacture, use or sale of “deferiprone” unless the information has been previously disclosed to the public with the consent of “Apotex.”⁵

This post-termination publication-ban period exceeded the normal one-year ban (as well as the two-year ban in exceptional circumstances) allowed by the University of Toronto Publication Policy. However, Drs. Olivieri and Brittenham were not investigators in this trial, its sites were not in Canada, and no patient in any hospital affiliated with the University of Toronto was enrolled in it. Also, the University’s Publication Policy referred to “research undertaken in the University.”⁶ Thus the University’s policy may not have been applicable. Nevertheless, we consider restrictions on communication of the type in clause 7 of the consulting contracts inappropriate for medical researchers. We are of the view that Dr. Olivieri and Dr. Brittenham should have insisted on removal of this restriction before signing. As leading members of the LA-02 steering committee, it was possible that information about risks could have arisen from the LA-02 trial and have been available to them, that would have been important to patients and physicians in other L1 trials to know of.

Dr. Olivieri should have submitted the consulting contract to the Hospital or the University for review but did not do so. Although this is not an excuse, it should also be noted that an uncontroversial finding of the Naimark Review was that, at HSC:

compliance with reporting requirements or expectations was not monitored, and lack of compliance was apparently common.⁷

(2) The LA-02 protocol

Although the consulting contracts with Drs. Olivieri and Brittenham for the LA-02 trial were not relevant to data generated in the Toronto trials (LA-01 and LA-03), the LA-02 protocol became relevant to the L1 controversy in

1998. Apotex stated in a 1998 document prepared for regulatory purposes that LA-02 was the “pivotal” trial for licencing and LA-01 and LA-03 were “supportive” studies to it.⁸ In fact, the LA-02 protocol stated:

1.0 BACKGROUND

...

The purpose of this protocol is to determine prospectively the incidence of agranulocytosis [severe loss of white blood cells] and other severe adverse events associated with therapy with Deferiprone.

2.0 OBJECTIVES

2.1 Primary Objective:

To determine the incidence of agranulocytosis and other severe adverse events with oral administration of deferiprone, 25 mg/kg body weight tid for a total daily dose of 75 mg/kg body weight, in a prospective one-year study of patients with transfusion-dependent thalassemia.

2.2 Secondary Objective:

To determine the efficacy of deferiprone in the treatment of iron overload in patients with homozygous β -thalassemia as assessed by serum ferritin concentration.⁹

Thus, the primary objective for the LA-02 trial was to assess safety in relation to the incidence of known acute-toxicity effects of the drug. This fact was outlined to patients enrolling in the trial, in the Informed Consent Form appended to the LA-02 protocol:

Over the past 5 years, approximately 500 patients between 2 and 85 years of age in 15 countries have taken a new iron chelator (L1, APO-66, Deferrum) for different periods of time. These studies have shown that L1 may reduce iron overload in the heart and the liver in patients receiving regular transfusions. Further studies are required to prove the efficiency of the drug. The purpose of this study is to determine the safety of L1 in the treatment of iron overload.¹⁰

In the LA-02 trial, the convenient but relatively inaccurate measure of iron overload, serum ferritin concentration, was used *instead* of the accurate measure, hepatic iron concentration (HIC), because this was a short-term trial in which efficacy was the secondary objective.* Among the inclusion criteria for LA-02 trial subjects was elevated level of either serum ferritin

*It is established in the literature that the only accurate measure of tissue iron stores is HIC, and that serum ferritin concentration, though convenient, is only an approximate measure and can be misleading. This was known to some investigators since the 1980s, and was emphasized by Dr. Olivieri in the protocols for her trials in Toronto from the outset. During the 1990s, additional studies confirmed the inaccuracy of serum ferritin concentration as a guide to iron-chelation treatment. For instance, Dr. Beatrix Wonke and her group, reporting in *Blood* (91,1, 1998) on their long-term L1 study, wrote, “Overall, the serum ferritin and chemical liver iron [HIC] values did not correlate.” It was considered safe to rely on serum ferritin concentration in the LA-02 because this was a study of only one year in duration. In the longer-term trials, LA-01 and LA-03, HIC was determined annually for each participant.

concentration, *or* HIC. In other words, unlike the protocols for the Toronto trials, the LA-02 protocol did not specify measurement of baseline HIC for every patient on enrolment. (The LA-02 protocol specified that HIC would be determined only in those cases of patients for which it was “indicated clinically by uncertainty about body iron stores.”)

The LA-02 protocol also did not specify baseline liver histology for every patient enrolled. In addition, the LA-02 trial, unlike the LA-01 trial, was not a randomized comparison trial, and its protocol did not specify the same complex array of monitoring tests as the LA-01 protocol. The LA-02 trial was completed in 1996, and majority of patients from it were then enrolled in “a long-term follow-up study” termed LA-06, with a protocol similar to LA-02.¹¹

Conclusions

1 | The Hospital and the University should have had a clear policy and a clear process to ensure that researchers did not sign contracts with inappropriately restrictive confidentiality clauses.

2 | Dr. Olivieri and Dr. Brittenham should not have signed a contract with a clause that could have been used to restrict communication of information about risks that could potentially have arisen. However, in fact, the LA-02 consulting contracts were not relevant to data generated in the trials in Toronto and it was not any data from the LA-02 trial that gave rise to the dispute. Dr. Olivieri wished to communicate findings from data of the LA-03 patient cohort, and it was these findings that Apotex attempted to deter her from communicating. As noted above, the LA-03 contract of October 1995 “supplanted” any earlier agreement on data from the LA-03 trial, and it contained no restrictions on communication of results.

3 | The primary objectives of the LA-03 and LA-01 trials included both long-term efficacy and safety, in the latter case in comparison to DFO. They both included baseline liver iron (HIC) and liver histology assessments for all participants. The primary objective of the LA-02 trial was safety in relation to known acute-toxicity effects of the drug. Neither LA-02, nor its follow-up trial LA-06, included baseline liver iron (HIC) and histology assessments for all participants. Therefore, unless subsequently modified so as to start from a baseline, this sequence of trials would be unlikely to scientifically assess long-term efficacy or identify liver damage.

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5C | Progress of the Toronto trials

(1) Encouraging data from the long-term trial (LA-03)

THE DATA ON the cohort of patients in the long-term trial continued to be encouraging in 1993 and 1994. By mid-1994 twenty-one patients in this group had been treated with L1 for an average of 3.1 years (the range was 1.0 to 4.8 years—the majority of these patients had been enrolled in the pilot study, of which LA-03 was the continuation). The drug continued to be effective in reducing body iron stores (as measured by HIC) in patients and no significant adverse effects had been observed. Drs. Olivieri, Brittenham, Koren and other members of their research group reported these results in April 1995 in the *New England Journal of Medicine*.¹ The article noted that in all eleven patients whose HIC was in a safe range when they were enrolled in the trial, L1 maintained HIC in a safe range. It also noted that in eight of the ten patients whose HIC was in an unsafe range when they were enrolled, L1 reduced HIC to a safe range, while in the other two patients HIC was substantially reduced from pre-trial levels.

Although the long-term trial was not a randomized comparison trial, it been running for a substantial period of time, the results were favourable and they were published in a journal of the highest standard. Thus, the 1995 article was influential in further encouraging hopes for the development of L1 as a treatment for iron overload. However, the authors noted that more investigation was needed before L1 could be recommended for therapy for iron overload.

(2) Progress of the randomized, comparison trial (LA-01)

The planned cohort size for this trial was sixty-six patients who would be randomly assigned to either of two treatment arms, one group to be administered L1, the other group to be administered DFO. Patients would be enrolled for a “2 year study period,” followed by a one year monitoring period “on the therapy to which they were randomized.”² Enrollment of the full cohort of patients took a considerable period of time, beginning in November 1993 and extending to September 1995.³ In order to attain a full cohort, seven patients were enrolled at the Montréal Children’s Hospital under the care of Dr. Geoffrey Dougherty.⁴ At the time Apotex terminated the trial on May 24, 1996, there were fifty-nine patients enrolled in Toronto and seven in Montréal.

As the trial progressed, amendments to the original (1993) protocol were proposed by the investigators and approved by the HSC REB (later, also by the Montréal REB). Some were put forward by Dr. Koren, others by Dr. Olivieri (in each case, also on behalf of the other investigators). For instance,

an amendment put forward by Dr. Koren in September 1995, proposed that for patients unable to travel to Cleveland for HIC determination by SQUID because of immigration status, HIC determinations would only be made by “the routine liver iron determination [i.e., by biopsy].”⁵ This was approved by the REB and then included in a list of recent amendments Dr. Olivieri reviewed with the REB Chair later that month.⁶

Although this trial had substantial Apotex and MRC funding, the ongoing requests for organized and analysed data made by Apotex caused a strain on the budgeted time and resources available to the investigators. Frustration with limited resources with which to respond to repeated Apotex requests for data began in late 1994, in regard to the unfunded LA-03 trial, but by mid-1995 extended to work on both trials. This was expressed by each of the investigators, Dr. Koren and Dr. Olivieri, in separate letters to Apotex in August 1995, in regard to the two trials, LA-01 and LA-03.⁷ It is relevant to note that, as Chair of the LA-02 Steering Committee, Dr. Olivieri was in frequent contact with the site investigators for that trial, and so knew that the LA-02 sites “were receiving significantly more support, for less work, than had been provided to the LA-01 and LA-03 trials.”⁸ Thus, in the draft budget she submitted to Apotex on May 20, 1996 for the renewal of the LA-01 contract (then still under active consideration by both Apotex and the investigators), she asked for funds for additional staff and other resources.⁹

5D | Concerns arising in 1995

REVIEWING PATIENT PROGRESS in January 1995, Drs. Olivieri, Brittenham and Koren became concerned that recent annual HIC determinations indicated that, in six of twenty-one participants in the LA-03 trial,* tissue iron burdens “had stabilized at levels higher than expected.”¹ Thus, the concern arose that the drug might be losing sustained efficacy in these six patients (the extent varied from one patient to another). They discussed this concern with representatives of Apotex and with REB Chair Dr. Stanley Zlotkin. Drs. Olivieri, Brittenham and Koren reviewed data from a variety of monitoring tests in an effort to identify causes. They considered several possibilities, including the following: whether the Apotex formulation of L1 might be different from that prepared by Dr. McClelland in the University’s Chemistry Department (during the pilot study, 1989–1993); body ascorbic acid status; iron excretion rates; and pharmacokinetic and metabolic properties of the drug. These considerations were inconclusive—for instance, L1 was “continuing to promote iron excretion,” and ascorbic acid levels were in a normal range for most participants.² This made clear that more extensive study would be required.

The discussions with Apotex during this period also involved the concern by the investigators that the LA-03 trial was underfunded. In February 1995, Dr. Olivieri requested additional financial support from Apotex to help with data collection and analysis, in the form of Apotex co-support for funding for an additional research fellow, to be combined with funds she hoped to receive through an application to the Cooley’s Anemia Foundation. Replying on March 7, Dr. Spino agreed in principle with the request for financial support, on the condition that the investigators provide data Apotex required for regulatory purposes retroactive to November 1994. In his reply Dr. Spino wrote:

The original agreement for the LA-03 trial was that Apotex would supply drug at no cost in exchange for information on the ongoing monitoring of the patients. Because the current protocol requires extensive monitoring of these patients, you have indicated that there is insufficient time to provide the information needed by Apotex for monitoring the trial. The result is that data have stopped coming to Apotex since November 1994. That puts us in violation of our agreement with the Health Protection Branch on this protocol. The Government is very clear—they allow us to provide an investigational drug, as long as we continue to monitor progress of the patients. Without the data we cannot monitor the patients which would force us to terminate the supply of the drug or risk the consequences of action by the Health Protection Branch. We understand your dilemma in not having sufficient resources to complete all the work that is currently required in the protocol.

*A total of twenty-six patients had been enrolled in the LA-03 trial since it began in 1989, but several had not remained enrolled for long enough to provide sufficient data to be included in a review of sustained efficacy of L1.

Therefore, we suggested that a revised protocol could be prepared with scaled down requirements for monitoring. There are several elements in the current protocol submitted to the Cooley's Anemia Foundation which appear unnecessary for safety but do require resources, and there are other elements we believe are of minimal value in safety assessment but do require substantive resources as well. It is our recommendation that the protocol be revised. We would be pleased to put the draft revision together for you.... the judgment, at this time, is that a scaled-down version of safety monitoring would be sufficient. Nevertheless, we are willing support your [funding] request because of our ongoing relationship.³

Dr. Olivieri replied to Dr. Spino on the same day, March 7, 1995, stating that the monitoring schedule already represented “the minimum level to ensure safety,” given the “experience in the unexpected toxicities of long-term chelation therapy.”⁴ Her reply suggested that the concern that arose in January 1995 from data indicating a possible reduction in sustained efficacy meant that monitoring should not be scaled down. She emphasized to Dr. Spino that the LA-03 patients formed a “sentinel cohort” for determination of the safety and efficacy of this as yet unproven drug.⁵

However, Apotex continued in the view that monitoring should be scaled down, and to this end the company drafted a major modification to the LA-03 protocol, to be submitted for ethics approval as “a complete protocol.”⁶ This draft protocol, dated April 28, 1995 and signed by a number of Apotex staff on various dates in April and May, was forwarded to Dr. Olivieri. The draft proposed a modification of “objectives and study procedures,” notably in that the objectives of the existing protocol, “efficacy and safety” would be scaled down to “safety,” and gave as a rationale Dr. Olivieri's 1995 article in the *New England Journal of Medicine* that was based on earlier data. The Apotex draft modification stated:

Recent data published by Dr. Olivieri (1995) and others indicate that efficacy of deferiprone as shown by decreased liver iron concentrations has been sufficiently established. Since it is expected that deferiprone will be a chronic use product, it is essential that long term safety of the product be prospectively assessed. This modification eliminates monitoring some of the measures of clinical efficacy but maintains those required for safety.⁷

A significant modification proposed by the company was:

Every 12 months patients will undergo the same pre-treatment assessments with the exception of the liver biopsies and SQUIDS.⁸

Thus, Apotex proposed to eliminate the procedures needed for the primary efficacy measure, hepatic iron concentration (HIC)—the recent data on which had given rise to the concerns of the investigators. HIC is also a critical *safety* measure because loss of efficacy could expose participants to the known risks of iron loading. Dr. Olivieri did not accept Apotex's proposal and in handwritten revisions to the draft, she added various measures, including

annual HIC determination.⁹ It resulted that no change to the 1993 LA-03 protocol was made at this time.

Beginning in March 1995 and over the course of the next ten months, Dr. Olivieri withdrew a total of eight patients from the LA-03 trial as results of their individual (annual) HIC determinations became available.¹⁰ These were patients who were observed to be at risk from iron overload, due to apparent ineffective chelation by L1.* Withdrawal from the study and transfer to deferoxamine treatment involved counselling patients that the onerous but proven standard therapy was essential in their case, because this trial cohort consisted of patients who had not been compliant with deferoxamine.

After the disagreement with Apotex over LA-03 monitoring procedures, Dr. Olivieri contacted Dr. Agnes Klein of the Health Protection Branch of Health Canada in June 1995 for advice on how to proceed. She reviewed with Dr. Klein the discussions to date on possible factors contributing to the reduction in sustained efficacy noted above. She noted to Dr. Klein that the patients enrolled in this trial had been non-compliant with standard therapy. Thus, except in cases where L1 had lost efficacy, attempting to transfer all patients from this group back to standard therapy on a permanent basis did not appear feasible. Dr. Klein's recommendation was that the existing protocol be amended to facilitate study of the reduction in efficacy.¹¹

Meanwhile, discussions over funding for LA-03 continued. In her March 7 reply to Dr. Spino, Dr. Olivieri outlined ways of continuing the existing levels of monitoring, until funds could be obtained, by re-allocating staff time and arranging to have some of the tests being performed by collaborating scientists to be done at reduced or no charge. She repeated her request (made in February) for Apotex co-funding in support of her application to the Cooley's Anemia Foundation.¹² Dr. Spino wrote back on March 8, endorsing Dr. Olivieri's application to the foundation, and confirming that if it were successful, Apotex would "provide an additional \$45,000" for the LA-03 trial. He added in this letter:

Your commitment to carrying out the highest level of clinical research is well recognized and is a major factor in supporting your application.¹³

The funding discussions extended over several months. Dr. Koren and Dr. Olivieri each wrote to Apotex in August 1995 expressing frustration over Apotex's requests for additional data and analysis in the face of inadequate resources, and saying that they were in fact continuing to supply the

*Dr. Olivieri reported this Committee of Inquiry that the records show that she withdrew patients from LA-03 in March, May, July, August and September 1995, and January 1996. She reported that three were withdrawn because their HICs were rising and five others because their HIC had stabilized in intermediate or high risk categories. (See section 5F for descriptions of iron overload risk categories.)

requested data despite the resource problems. In his letter to Apotex, Dr. Koren wrote

We believe there is no basis on which to imply that the investigators of this study [LA-03] have *any* responsibilities [for provision of data to Apotex] that are not being ‘adequately met’ but would welcome further thoughts on this from you.¹⁴

The dates on which trial participants had their annual HIC determinations were spread over the course of the year, depending on the dates of their initial (baseline) assessments. By July 1995, the number of LA-03 participants with HIC levels indicating a possible reduction in sustained efficacy of the drug had increased from six to eight, and by August this number had increased to ten (out of a total of twenty-one*). In view of the trend indicated by the 1995 HIC data points obtained up to late July, Dr. Olivieri concluded that a modification of the existing protocol would not be sufficient. She proposed to Apotex that a new protocol be developed, incorporating “detailed plans for optimal follow up, testing and management to adequately protect these patients,” and “addressing the inclusion of monitoring for this unfortunate development [the recent HIC data showing possible reduction in sustained efficacy].”¹⁵ Dr. Olivieri added that “Gidi [Dr. Koren] is in agreement,”¹⁶ and that the investigators understood that this proposal would have resource implications.

Dr. Olivieri wrote to Apotex again in August, enclosing a summary analysis on the HIC data to date, including two graphs showing annual HIC value for each patient as a function of time—one graph for the ten patients showing signs of reduction in sustained efficacy, the other for the eleven patients for whom the drug continued to be effective. She said that she would be advising the REB of this data and her analysis of it. The analysis Dr. Olivieri attached indicated that the trend observed in the recent data points was of increasing concern, but did not yet constitute an “adverse event.”¹⁷ Her analysis stated that:

[T]he long-term treatment cohort... have received deferiprone because of unwillingness or inability to administer deferoxamine.... 21 patients have undergone more than one year of therapy and have undergone at least two evaluations of hepatic iron concentration [HIC].... Of concern, the most recent assessment of hepatic iron concentration in 10 of these patients... has shown a reduced response to deferiprone over time.... Because deferiprone is an experimental drug with a high risk/benefit ratio related to its most serious adverse effect, agranulocytosis, our recent and unexpected findings indicate that

*This total includes patients who had been in the trial but had been withdrawn, in addition to the number still enrolled—those for whom sufficient data was available for an analysis of sustained efficacy.

continued, careful follow-up of all patients receiving deferiprone cannot be relaxed in this only long-term treatment cohort of patients ...¹⁸

Dr. Spino replied a week later, expressing doubt about Dr. Olivieri's analysis and interpretation of the data, and demanding "the raw data ... to carry out our own data and statistical analysis," otherwise, "we have no option but to accept your preliminary assessment and consequently terminate the LA-03 study."¹⁹ This response from Dr. Spino resulted in signs in the correspondence of a strain in relations between the investigators and Apotex.²⁰ However, meetings and correspondence continued among Drs. Spino, Olivieri and Koren in late August and in September, 1995, with a view to Apotex providing funds for LA-03, and to developing a new protocol to study the reduction in efficacy observed in some patients.²¹ By copy of her letter to Dr. Spino of September 15, Dr. Olivieri informed the REB Chair Dr. Zlotkin of the concern over findings in the LA-03 cohort, and the lack of funding for this study. She wrote, "I have drafted a single protocol that incorporates the approach to identification and correction of the etiology of the loss of sustained efficacy..." and added that, "A full budget will accompany this protocol."²² On September 18, Dr. Olivieri sent the raw data to Apotex, and enclosed a new draft protocol (termed LA-05) which included additional tests for the purpose of studying the observed "loss of sustained efficacy" in some patients.²³ She also enclosed a budget.

Also on September 18, as well as a few days earlier, Dr. Olivieri met with REB Chair Dr. Zlotkin to review her "concerns regarding the ongoing studies of deferiprone."²⁴ These included her recent concern arising from the long-term (LA-03) trial on reduction in sustained efficacy of the drug in some participants, and the measures she proposed for addressing this concern. Dr. Olivieri also reviewed with Dr. Zlotkin a series of minor amendments to the LA-01 protocol (some of which he had already approved). In addition, she discussed her concern about what she considered to have been a suggestion by Apotex that the LA-01 trial proceed with a cohort smaller than the 66 specified in the design of that trial. Dr. Zlotkin provided a number of "thoughtful suggestions."²⁵ A few days later, on September 22, Drs. Olivieri and Koren had a meeting with Dr. Spino that "seemed to resolve most of the issues."²⁶

Two developments emerged from the various discussions involving Dr. Olivieri, Dr. Koren, Dr. Zlotkin, Dr. Spino, and also Dr. Brittenham. First, pending agreement between the investigators and Apotex on sponsorship of a new trial protocol proposed by Dr. Olivieri (LA-05) and ethics review of it, Dr. Olivieri and Dr. Koren drafted modifications to the LA-03 protocol and submitted the modified protocol to the REB. This document gave express recognition to the recent concern that the drug may have lost sustained efficacy in some trial participants, and said:

Factors contributing to the possible loss of sustained efficacy will be defined in a separate protocol.²⁷

Second, on October 2, 1995, Dr. Spino signed and issued the LA-03 contract.*It was later signed by Drs. Koren and Olivieri (on October 10 and 12, respectively). In this contract Apotex acknowledged, in principle, that there could be an inadequate response to the drug in some patients, and undertook to work with Dr. Olivieri to reach agreement on a new protocol to be submitted to the REB for approval. The contract also confirmed that hepatic iron concentration was the principal measure of efficacy of the drug:

A detailed analysis of patients responding to L1 in the LA-03 trial is merited. We will complete a careful assessment of the liver iron values [HICs] in each patient over time and compare this with information we can obtain relating to responses to DFO in thalassemic patients.²⁸

This contract provided funding for the LA-03 trial for the next two years, at an annual rate comparable to the level of the one-year terminal MRC grant for 1992–1993 had provided for the pilot study (the study that continued as LA-03), plus additional funds to study loss of response in “those patients where there is mutual agreement that the response to L1 is inadequate.”²⁹ As noted in section 5A, two other important features of this contract were that:

- (i) it contained no confidentiality clause; and
- (ii) it gave Apotex the right “to terminate the LA-03 study.”³⁰

The day after issuing the LA-03 contract, Dr. Spino wrote to Dr. Brittenham, acknowledging that:

you have both the expertise in iron disposition and the data to help us sort out this issue [loss of efficacy of L1].³¹

Among other things, Dr. Spino requested Dr. Brittenham’s data on DFO, so that the efficacy of the two drugs could be compared. Discussions involving Dr. Brittenham, Dr. Olivieri and Dr. Koren, and Apotex about the loss of response in some patients and about the draft of a new protocol then proceeded over the next few months. However, by early 1996, Apotex still did not accept that the observed loss of response was as extensive in the cohort, or as significant, as Dr. Olivieri and Dr. Brittenham maintained.³²

*This contract included two paragraphs clarifying understandings about the LA-01 trial, but its principal provisions concerned LA-03. In particular, the contract: expressly provided “Funding for LA-03 ... to enable adequate support staff to maintain records and provide Apotex with the information they require for Regulatory purposes;” and funding to study patients identified as “inadequate responders;” and concluded with the provision, “There are no other costs related to the LA-03 trial ... Therefore, this agreement supplants any other previous agreement on this cohort of patients.” Appended to this contract was a “SCHEDULE OF PAYMENTS TO HSC FOR LA03 STUDY.”

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5E | Identification of the first risk

BY EARLY 1996, the number of LA-03 participants whose recent HIC data indicated a loss of sustained efficacy had increased to twelve out of a total of nineteen.* This continuation of the unfavourable trend heightened concerns and Dr. Olivieri, in collaboration with Dr. Brittenham, prepared an analysis. They considered not only the graphs of annual HIC against time for each patient (over the 2 to 6.5 years they had been on L1), and overall statistical trends for the cohort as a whole and in subgroups, but also grouped patients into *clinical risk* categories based individual HIC levels and on the medical literature on the effects of iron overload. The grouping was as follows:

1. In seven (7) patients, hepatic iron concentration has been reduced or maintained in a range considered to be clinically desirable.
2. In three (3) patients, hepatic iron concentrations increased during therapy with defeniprone
3. In three (3) patients, hepatic iron stabilized at concentrations associated with a greatly increased risk for iron-induced complications and death (hepatic iron exceeding 15 mg per gram dry weight liver tissue)
4. In six (6) patients, hepatic iron stabilized at concentrations greater than those considered desirable (hepatic iron exceeding 7 mg per gram dry weight liver tissue)... .¹

Dr. Olivieri reported to us that she concluded that the situation in February 1996 was such that the Research Ethics Board should be formally advised of the data and her analysis of its possible clinical implications, with her recommendation that the patients be informed. She reported that Dr. Brittenham, a hematologist and an expert in disorders of iron metabolism, agreed. The risk/benefit ratio of L1 for this cohort of patients, who had been noncompliant with standard therapy, was seen to have changed significantly in the most recent HIC data: there was now a greater risk of the chronic toxicity of iron loading. A change in the patient information and consent forms would provide them with an opportunity to consider whether they wished to remain on L1, or start standard therapy despite its onerousness.

Dr. Olivieri forwarded the data and the analysis to Apotex on February 5, 1996 and a meeting was held on February 8 involving Drs. Olivieri, Brittenham and Koren, and Dr. Spino and other Apotex personnel. During the meeting, Dr. Olivieri and Dr. Brittenham outlined factors involved in iron

*Reports by Dr. Olivieri in 1995 used a total of twenty-one; the difference in the numbers appears to be due to the fact that two patients had a less severe form of thalassemia, so their data was not considered in the 1996 report to the REB, as Dr. Olivieri noted in that report. By February 1996, eight of these nineteen were no longer in the LA-03 trial, having been withdrawn by Dr. Olivieri in 1995 (see section 5D).

disposition and the medical risks to trial participants associated with HICs in various ranges. The minutes of the meeting record that the interpretation of the data presented by Dr. Olivieri and Dr. Brittenham “differed from that of the sponsor [Apotex],” and that “Dr. Spino stated that, based on the liver iron data, it appeared to him that about 75% of the patients were responding adequately to deferiprone.”² Dr. Spino also noted that the LA-03 cohort consisted of patients who had been noncompliant with standard therapy, so that, “In light of there being no alternative therapy, it would appear that the response noted for deferiprone in the LA03 trial was certainly meritorious.”³ Dr. Olivieri replied that some patients on L1 “actually could take DFO [standard therapy],”⁴ and suggested that information on the loss of response should be disclosed.

The only persons present in the meeting on February 8, 1996 with the relevant expertise to assess the medical issue of risk to patients were Drs. Olivieri and Brittenham. On the basis of their clinical experience and expertise, and their understanding of the literature, they judged that a risk had been identified. Of the others present, Dr. Koren, who was not an expert in relevant fields, appeared to support their judgment. Dr. Spino and the other Apotex staff, who were reliant on Drs. Olivieri and Brittenham for medical and scientific expertise (as is clear from Apotex documents cited earlier in this report), did not accept their judgment in this matter. The identification of this medical risk depended both on relevant expertise, and an acceptance of the criterion for efficacy of the drug specified in the trial protocol, that the principal measure of efficacy was HIC and that it was an endpoint measure. It was important that high HIC levels be lowered to a safe level, and maintained at a safe level.

The disagreement centred on the medical implications for patients of their HICs being in certain categories. The medical implications for patients of iron-loading are complex and a high level of expertise in hematology, internal medicine and iron metabolism is required to assess the risks to patients. Apotex did not have staff with the required expertise to appropriately contest the identification of medical risk.

After the February 8 meeting, on February 12, 1996, Dr. Spino faxed a letter to Dr. Olivieri. It indicated Apotex’s disagreement with her interpretation of the data, but stated that, Apotex “agree[d] that some patients [were] responding inadequately,”⁵ and that, “We concur with you that these data need to be presented to the Ethics Committee.”⁶ He added that Apotex would undertake further analysis, but in the meantime would postpone a scheduled visit to Ottawa (i.e., to HPB), would advise the LA-02 investigators to interrupt plans, and would “convene an independent Panel to evaluate the data you presented.”⁷

That same day (February 12), Dr. Olivieri wrote to Dr. Spino to confirm her intention to report to the REB that there was risk of loss of sustained efficacy. The report she attached (intended ultimately for the REB) noted that studies published to date (including her own 1995 paper in the *New England Journal of Medicine*) had shown L1 to be effective over shorter time periods and that the only adverse effects known previously were acute toxicities observed only in small numbers of patients. The report outlined the risks to patients from chronic iron toxicity associated with elevated ranges of HIC (quoted above). It also noted that as a result of the early favourable indications, L1 was now being used in other trials involving 253 patients (in LA-01 and LA-02), and that the new risk determined from LA-03 data may be relevant to these trials. Dr. Olivieri's report concluded:

... these observation [sic] of variation in therapeutic response to deferiprone suggest the need for continued assessment of the balance between risk and benefit in patients treated with this drug.⁸

Within two days, Apotex had re-examined its position. On February 14, Dr. Spino wrote that Apotex was "even more certain that the data do not support a change in effectiveness at this point in time."⁹ Further, Apotex now felt it "premature" for Dr. Olivieri to report her interpretation to the REB as this "may alarm the [REB] unduly and prior to the time that the claims can be substantiated."¹⁰ Dr. Spino proposed that her report to the REB be re-drafted so as to incorporate a series of wording changes to the text. Notably, he suggested that the report be re-cast as an "interim report... to summarize the observations associated with the variability in response." Dr. Spino's letter went on to explain that, "we are concerned that the impression generated from your submission to the Committee [REB] may trigger an unwarranted decision," and added, "we cannot support your position with the data presented to date."

Had Dr. Olivieri acceded to Apotex's proposal, she would not have been informing the REB of a risk to patients that she had identified as a result of her analysis of the data. In such an event, she would not have fulfilled her ethical obligation to patients in the trial. However, she did not accede to Apotex's proposal. In a reply to Dr. Spino on February 15, Dr. Olivieri expressed a willingness to include Apotex's recent letters to her when she submitted her report to the REB. She offered to review her findings once more with Apotex, but added that "a report regarding this loss of efficacy" must soon be sent to the REB.¹¹ Dr. Spino responded in a letter the next day:

We see no convincing evidence that there has been any change in activity [effectiveness] from the time you published the remarkable findings of the effectiveness in the long term treatment cohort we now refer to as LA03.¹²

Here Dr. Spino was referring to Dr. Olivieri's article that appeared in the *New England Journal of Medicine* in April 1995, based on data up to mid-1994. The data showing loss of sustained efficacy was obtained from

monitoring of patients during the year and a half since that article was submitted. Dr. Spino had been provided with all of this additional data and explanations of its significance. Moreover, he himself went on in the same letter to acknowledge that the new data showed that there were “patients with suboptimal responses” and that “it would be advantageous to determine how we can enhance the response to deferiprone in these poor responders,” a point with which Dr. Olivieri agreed. However, a fundamental Apotex objection to Dr. Olivieri’s findings was clearly enunciated in this letter:

We strongly disagree with the conclusions of decreasing effectiveness leading to a need to reconsider the risk benefit ratio of the drug in thalassemic patients based on the information we have to date.¹³

Reconsideration of the risk/benefit would almost certainly necessitate informing patients of an unexpected risk and providing them with an opportunity to decide whether they wished to remain in the trial.

On February 29, Dr. Olivieri wrote to Dr. Zlotkin that a detailed report of her concerns regarding loss of efficacy of L1 would be transmitted shortly, after a further discussion with Apotex.¹⁴ She sent her report to the REB on March 5.¹⁵

Between mid-February and late May 1996 there was extensive correspondence involving Dr. Olivieri, Dr. Spino, Dr. Zlotkin and Dr. Koren. Having failed to dissuade Dr. Olivieri from reporting her findings, Dr. Spino made repeated efforts to persuade the REB that she was mistaken in her interpretation of the data. He forwarded Apotex’s view of the LA-03 data to Dr. Zlotkin on March 15.¹⁶ Dr. Zlotkin met with Dr. Olivieri on March 25, at her request, to discuss her findings, Apotex’s disagreement with them, and courses of action.¹⁷ Dr. Zlotkin replied that day to Dr. Spino’s March 15 letter, stating, “As you know, the Research Ethics Board does not act as an intermediary... Consequently, your correspondence should be directed to Dr. Olivieri for resolution.”¹⁸ He added that he had received her report and would be asking her to amend the patient consent forms.

Responding to Dr. Olivieri’s report on April 9, 1996 in his capacity as REB Chair, Dr. Zlotkin directed her to do the following:

- provide a revised information and consent form for LA-03 patients for review by the REB
- report the unexpected finding to the Health Protection Branch (the Canadian regulators)
- inform all physicians responsible for the clinical care of the patients in the LA-03 trial, regardless of whether these individuals are collaborators in this study

- notify the Ethics Committees of each hospital in which these (LA-03) patients receive their clinical care (if the Committees issued approval for the study based upon the present information and consent forms—the relevant hospitals were HSC and TTH)
- ensure that appropriate diagnostic measures to evaluate continued efficacy of L1 are instituted in a timely manner and submit a separate protocol under which these measures are undertaken to the REB
- ensure that appropriate diagnostic measures are in place to evaluate the continued efficacy of L1 in the other trial for which she was principal investigator, LA-01
- inform the study sponsor of the requirements set out by the REB.¹⁹

Apotex suggested that in issuing this directive without first having a full meeting of the REB, Dr. Zlotkin might not have been acting appropriately.²⁰ However, the existing procedures permitted the Chair to act alone in special circumstances and report later to the full REB.²¹

Dr. Spino next wrote to Dr. Koren, on April 18, inviting him to intervene, not only with Dr. Zlotkin but with the full REB, to obtain at least a delay in implementation of Dr. Zlotkin's directive to Dr. Olivieri:

I understand you [Dr. Koren] also do not concur with the view that there is a general lack of response to L1 in the LA-03 subjects. As Co-Investigator, you may wish to convey your view to Dr. Zlotkin.

...he [Dr. Zlotkin] appears to be taking a decision on partial information and that decision has ramifications well beyond the Hospital for Sick Children or its patients.

... it is premature to take any action with the LOR [Loss Of Response] patients, except possibly to study those three in whom there appears to be some decreasing level of effectiveness. In addition, there are both Regulatory and resource implications associated with Dr. Zlotkin's letter [to Dr. Olivieri, April 9] that will have a bearing on any action we might take. I am not sure that it is appropriate that he make a decision of this nature without a full meeting of the Ethics Board and a thorough review of the data from the Advisory Committee.²²

Dr. Spino wrote directly to Dr. Zlotkin again on May 2, at greater length and expressed his views more forcefully than in earlier correspondence:

[Y]our letter of April 9, 1996 instructs Dr. Olivieri to take certain actions which, we believe are inappropriate, because they are based on decisions made with inadequate information.²³

He then proceeded to dispute in detail a number of the points in Dr. Zlotkin's letter (cited above). Dr. Spino added that the LA-02 investigators felt that Dr. Olivieri's "information did not warrant notification of their REBS," and that:

This same view was expressed by Dr. Koren, a co-investigator in the LA03 study, who stated in a meeting on February 29, 1996, with Apotex, Dr. Olivieri and Dr. Brittenham, that in his opinion, this information was the type that might be included in an annual report to the REB, rather than an urgent report noting “unexpected” findings.²⁴

Dr. Spino concluded:

We trust you will agree that the actions which have already been taken by Apotex constitute a full and complete response to the situation and *no further action by Dr. Olivieri at this time is warranted.*²⁵ (emphasis added)

The unmistakable import of the last phrase is that Dr. Olivieri should not inform patients, or others with a right or need to know, about the new risk. Indeed, several weeks later, Apotex stated in writing that its concern was that Dr. Olivieri be prevented from informing patients of her findings (in a letter from Dr. Spino to Dr. Brittenham—see section 5F).

Dr. Zlotkin’s response to Dr. Spino on May 10 was clear:

I understand how important this research is to you but you must understand I take my direction from the principal investigator concerning unexpected findings. *My mandate is to protect study subjects and patients and to that end must ensure full disclosure* when unexpected study findings are identified.²⁶ (emphasis added)

On May 20, 1996, Dr. Olivieri provided revised patient information and consent forms for LA-03 and LA-01 to the REB and to Apotex.²⁷ A covering letter to patients and parents by Dr. Olivieri summarized the new information:

Unexpectedly, recent studies of patients enrolled in this long-term trial have found that the body iron has continued to fall to, or been maintained at, acceptable levels *in only a minority of patients.** ... The explanation for this apparent loss of effectiveness of deferiprone is unknown.²⁸ (emphasis in original)

Conclusions

1 | We conclude that Dr. Olivieri and the REB Chair, Dr. Zlotkin, conducted themselves appropriately. As data leading to the identification of the risk was developed during 1995, Dr. Olivieri informed the manufacturer, the regulators and the REB through correspondence and discussion. Beginning in March 1995, she withdrew patients from the LA-03 trial when their annual HIC determinations indicated they were in categories of significant risk

*This was the essence of the detailed information discussed with Apotex on February 8, 1996. Another long-term study of L1 by the group of Drs. V. Hoffbrand and B. Wonke in England published essentially the same conclusion later that year. Both Dr. Olivieri and the English investigators presented their abstracts in the December 1996 ASH meeting. In their abstract, published in *Blood*, the English group reported, “We conclude that long term iron chelation with L1 alone is successful at maintaining body iron at a ‘safe’ level *in only a minority of transfusion dependent patients.*” (emphasis added)

regarding iron overload. In late September 1995 she submitted a revised protocol for the long-term trial (LA-03) taking the new concern into account. She also prepared a new (LA-05) protocol intended to determine the reasons for the observed loss of sustained efficacy in some patients, and endeavoured to persuade Apotex to sponsor a trial on this basis. In early 1996 she provided Apotex with a report containing the data on the finding of loss of sustained efficacy, and in it she outlined the medical risks to patients. She also reported these findings to the REB and met with the REB Chair to discuss the situation. Thus she complied with her ethical and legal obligations.

Dr. Zlotkin provided suggestions on courses of action to Dr. Olivieri in their September 1995 meeting. In April 1996, on receiving her report that a risk had been identified, he directed her to do that which was required by law and by ethical guidelines governing research involving humans. As he told Dr. Spino, his responsibility was to protect study subjects and patients.

2 | We conclude that Apotex did not conduct itself appropriately—it acted in its own interests, with disregard for patient safety and autonomy:

a) Apotex tried to interfere with REB process. When it was rebuffed by Dr. Zlotkin, it tried to enlist Dr. Koren to intervene with Dr. Zlotkin and with other REB members. It then wrote to Dr. Zlotkin telling him his action was inappropriate, disputing his directives to Dr. Olivieri, and implying he should not have required Dr. Olivieri to advise patients of the risk she had identified. Thus, in pursuit of its own ends, Apotex tried to influence the REB Chair, Dr. Zlotkin and, when it did not succeed, disputed the authority of his office and impugned his judgment in fulfilling the obligations of his office.

b) Apotex obfuscated the issue by framing it as a scientific difference of opinion²⁹ and misrepresenting Dr. Olivieri’s conclusion. First, in a letter to the REB, Apotex argued that Dr. Olivieri was mistaken as (in its view) there was no “general loss of response” to L1 in LA-03 subjects.³⁰ On this basis the company argued that Dr. Olivieri was wrong about the science. However, Dr. Olivieri had not claimed a general lack of response. Rather, she had claimed that a majority of patients in the LA-03 cohort were showing a loss of sustained efficacy with long-term use of L1 and she therefore had an obligation to inform research subjects that there was a risk. Second, Apotex did not have the expertise to disagree with Dr. Olivieri on the matter of the medical risk to patients. Lastly, but of central importance, the issue was one of research ethics, of an obligation to inform research subjects of a risk that had been identified so they could decide on their continued participation. Whether or not there was a scientific disagreement could diminish neither the right of trial participants to be informed of a risk identified by the investigator nor the obligation of the investigator to inform them.

3 | It was during this period (the first half of 1996), that the first indications arose that Apotex understood Dr. Koren to be supporting its view, whereas he continued to maintain to Dr. Olivieri that he supported her findings. Notably, in a letter to the REB on May 2, 1996, Apotex used the purported opinion of Dr. Koren that Dr. Olivieri's finding of an unexpected risk did not warrant a special report to the REB. In the documentary record available to us, this was one of the first instances where Apotex used Dr. Koren's purported views to counter findings of risk by Dr. Olivieri. It is relevant to note that, unlike Dr. Olivieri, Dr. Koren is not an expert in the fields of medicine required to assess risks of iron chelation treatment in patients with thalassemia major (see section 2).

5F | Trial terminations and legal warnings

DESPITE SERIOUS DISAGREEMENTS, discussions continued into May 1996 on renewal of the LA-01 contract, which had expired on April 23, 1996. The contract specified that each patient would be treated for two years, but it took until 1995 to enrol the full cohort of sixty-six patients specified in the trial design. Thus, when the contract expired, some patients had been enrolled for less than the two years, and the trial was not yet complete. Dr. Spino wrote to Dr. Olivieri on May 8, 1996 indicating that re-negotiation of the LA-01 contract was contingent simply upon Apotex receiving the itemized budget for the continuation of LA-01, and approval of revisions to the LA-03 protocol.¹ There was no suggestion of terminating the LA-01 study. (The contract for the LA-03 study, which provided two years of funding from October 1995 onward, was still in force.) Dr. Spino concluded:

I look forward to receiving, at your earliest convenience, the new budget and we will review it promptly.²

Dr. Olivieri prepared a draft budget for a two-year extension of the LA-01 trial and forwarded it to Apotex on May 20, the same day she sent the revised patient information and consent forms to the REB, with copies to Apotex.³ Four days later, on May 24, 1996, Apotex wrote to Drs. Olivieri and Koren to inform them that it was terminating both the LA-01 and LA-03 clinical trials:

Effective immediately, the deferiprone clinical trials LA-01 “Randomized trial of L1 and Deferioxamine in Thalassemia Major” and LA-03 “The Long Term Efficacy and Safety of Deferiprone in Patients with Thalassemia” are being discontinued at the Hospital for Sick Children and The Toronto Hospital, General Division.⁴ *

In the same letter, Apotex warned Drs. Olivieri and Koren not to disclose information “in any manner to any third party except with the prior written consent of Apotex,” and warned that it would “vigorously pursue all legal remedies in the event that there is any breach of these obligations” it claimed they had under “paragraph 7 of the LA01 Agreement and the LA01 and LA03 Protocols.”⁵ **

Other than the fact that the LA-01 agreement had expired on April 23, 1996 no further explanation was given in the termination letter. The letter also notified Drs. Olivieri and Koren that all quantities of L1 in the hospital

*By this time, adult thalassemia patients were receiving their care in TTH.

**The relevant clauses in the LA-01 contract and the LA-01 and LA-03 protocols were quoted in section 5.A. Of these, only the LA-01 contract had a clause that would allow Apotex to prevent communication about an unexpected risk. The LA-03 contract had no such clause—Dr. Spino did not mention this contract in his letter.

pharmacy “must immediately be returned” and that Apotex would “contact the pharmacy directly to arrange for retrieval of the drug.”

In a separate letter to Dr. Olivieri on May 24, Apotex terminated her LA-02 consulting contract, effective immediately. No reasons were given. Apotex reminded Dr. Olivieri of her confidentiality obligations under this agreement and said any breaches of this obligation by her would be vigorously pursued.⁶ That same day Dr. Spino recorded a telephone message on Dr. Olivieri’s voice-mail:

Hi Nancy. I’m sorry we didn’t get a chance to meet face to face. It’s Mike Spino. I’ve left you an envelope. I’m sorry but *Apotex has decided to terminate the L1 studies* at The Hospital for Sick Children. We will not be renewing your contract for the LA-01 and LA-03 studies. *We will be closing out the patients from the study.* We are also terminating the contract with you pertaining to the LA-02 study and you will no longer be part of the LA-02 steering committee and your position as chairman on that committee will be replaced by another committee member. Nancy, I want to remind you of your confidentiality requirements under the contract. *You must not publish or divulge information to others* about the work you have done with Apotex including any data you may have gathered since April 23, 1993 pertaining to the use of Apotex L1 product without the written consent of Apotex. Now, *should you choose to violate this agreement you will be subject to legal action.* We’ve notified HPB about the action we are taking. It will be necessary to conduct close out assessments on all of the *patients* and they will have to be informed that the study is being closed out. *They need only to be advised that Apotex has decided that this is the best thing to do* at this time. They should be informed that plans are to continue to the development of L1 and that *we have every intention of bringing it to market as soon as possible. We advise you not to give them any incorrect information including, as you have stated, ‘the drug is working in only a minority of patients.’* This was in your draft letter to them. *This information is incorrect as verified by other investigators and if you in any way attempt to convey it you will be subject to legal action.* The thalassaemic community will be informed. We will do that but you are not to communicate your misinterpretations of these data without a written consent. Nancy, if you want to reach me this weekend you can but please read the letters first. Bye.”⁷ (emphasis added)

Like the letters, the telephone message provided no reason for this precipitous action. However, Apotex did state a reason to the Bureau of Pharmaceutical Assessment of the Health Protection Branch (HPB) of Health Canada:

On May 27, 1996 Apotex informed the Bureau that we had terminated the studies at Dr. Olivieri’s site following numerous problems with the

investigator, culminating in *her desire to modify the informed consent form* to indicate that deferiprone worked in only a minority of patients.”⁸ (emphasis added)

In a letter to Dr. Brittenham a few weeks later, on June 17, 1996, Dr. Spino confirmed that this was the reason for terminating the trials:

Previously, I explained to you that, based on the position that Nancy took (that the drug was working only in a minority of patients, and that it was losing its effect in some patients within 1-2 years), we felt it was no longer appropriate to conduct trials with her as the Principal Investigator. Since we did not concur with her assessment of the drug’s effectiveness, *we could not allow such information to be transmitted to patients*, thus misinforming them. In addition, we could not justify Nancy as the Principal Investigator in studies of a drug that she does not believe works.⁹ (emphasis added)

No other reasons were given for the terminations of the Toronto trials and the contracts with Dr. Olivieri. The letter went on to invite Dr. Brittenham (whose LA-02 consulting contract had not been terminated) to continue his “involvement with Apotex in the development of L1,” provided he “maintain ... confidentiality.”

The rationale for terminating the trials, namely, that the investigator Dr. Olivieri “did not believe” in the drug, is untenable. First, researchers are not required to “believe” in a drug under study; requiring faith in a drug under study flies in the face of an essential element of clinical trials, i.e., clinical equipoise.¹⁰ Second, there is no evidence that Dr. Olivieri was biased against the drug. Instead, she had identified a risk of loss of efficacy and was therefore obligated to inform patients. In fact, she wished to continue exploring the drug to determine, among other things, reasons for the loss of efficacy in some patients, as is clear from the documentary record of correspondence involving Apotex, Dr. Olivieri and the REB in 1995 and 1996. Moreover, Dr. Spino had been reminded of Dr. Olivieri’s position shortly before he wrote to Dr. Brittenham, at the mediation meeting Dean Aberman convened on June 7. Dean Aberman reported, “Nancy wanted to continue the L1 trial for two reasons—to continue the study of effectiveness/loss of effectiveness and ensure patients on L1 would continue receiving the drug.”¹¹

Later in 1996, on August 22, in one of his subsequent letters conveying a legal warning to Dr. Olivieri, Dr. Spino briefly re-visited the matter of reasons for terminating the trials. He wrote,

... your statement [in a draft conference abstract on LA-01 data] that the study was discontinued prematurely is incorrect. The study has been terminated at the Hospital for Sick Children, both for ethical and procedural reasons, but it continues at the Montréal Children’s Hospital.¹²

We do not know what Dr. Spino intended here by “ethical and procedural reasons,” but these sentences raise a serious question about scientific standards employed by Apotex, since a research trial designed for a cohort of 66 participants who were randomized to two treatment arms could not reasonably be expected to continue with only 7 participants.* After the cohort had been reduced to 11% of its designed size, it would no longer be able to answer the scientific question of how L1 compared to DFO as a treatment.

In February 1997 Dr. Spino gave a public explanation of why the trials were terminated. His statement was consistent with the reason conveyed by Apotex to HPB in May 1996, and with the reason stated in his June 1996 letter to Dr. Brittenham.¹³ He wrote to the editor of *The Medical Post*:

Unfortunately, Dr. Olivieri... approached the chair of the Research Ethics Board (REB) to obtain his agreement to modify the consent forms. Since Apotex believed the changes demanded by Dr. Olivieri would misinform patients regarding this therapy, we requested that the matter be evaluated by the full REB. The chairman of the REB refused to consider our request and this led ultimately to the termination of the studies.¹⁴

In August 1997 Dr. Spino wrote to Dr. Olivieri:

As you well know, the trial was discontinued because of unilateral and precipitous actions taken by you without regard for the views and opinions of Apotex scientific personnel or other experts and investigators in our trials.¹⁵

Dr. Spino did not specify in this letter what he meant by “unilateral and precipitous actions.” However, from the extensive correspondence during the months preceding the trial terminations the only reasonable inference that can be drawn is that he meant Dr. Olivieri’s decision to fulfil her obligation to inform the REB of the risk she identified, and her subsequent revision of the informed consent form as directed by the REB Chair.

Apotex’s position on why it terminated the trials changed significantly over time. In submissions to regulatory authorities in early 1998, the company alleged that Dr. Olivieri had committed serious protocol violations which “limit[ed] the quality of the data” from the LA-01 and LA-03 trials,¹⁶ and that this was “the

*The main site for the randomized trial (LA-01) was in Toronto. When the trials in Toronto were terminated, 59 patients were enrolled at the Toronto site and 7 at the Montréal site. On July 15, 1996 Dr. Olivieri and Dr. Koren wrote a joint letter to the LA-01 site investigator at the Montréal Children’s Hospital, Dr. Geoffrey Dougherty, to advise him that Apotex had terminated that trial at the main site in Toronto and that, “The 59 patients entered into this trial at the ... Toronto site have therefore been withdrawn from the study.” Their letter continued, “this development may place the seven patients in Montreal out of the context of a study that has sufficient statistical power to answer the scientific question posed by the original study. The reduction in numbers from 66 to 7 should probably need to be indicated to the Research Ethics Board of Montreal Children’s Hospital.”

primary reason the Sponsor decided to terminate the study at the Toronto sites on May 24, 1996.”¹⁷ Dr. Spino made similar allegations in a letter dated August 31, 1998 to HSC President and Chief Executive Officer Mr. Michael Strofolino. (See sections 5L and 5U.)

Given the substantial evidence to the contrary, the later allegations that it was protocol violations that resulted in the termination of the trials are unconvincing.* First, in its 1998 letter to Mr. Strofolino, Apotex even stated that, “the vast majority of the [alleged] protocol violations were detected following termination of the study.”¹⁸ Second, Apotex was negotiating an extension of the LA-01 contract until the revised patient information forms were submitted to the REB, and had executed a two-year contract to continue the LA-03 trial only a half year before this. Third, as noted above, Apotex stated to each of HPB (May 1996), Dr. Brittenham (June 1996), *The Medical Post* (February 1997), and HPB again (February 1997) that it terminated the trials to prevent Dr. Olivieri from disclosing a risk to patients, giving them no other reason. Fourth, Dr. Spino wrote to Dr. Olivieri in August 1997 to similar effect. Fifth, these new allegations did not surface until long after the trials were terminated, and they clearly served Apotex’s interests. Sixth, if the alleged protocol violations compromised the data (as Apotex alleged to regulators in 1998), then Apotex should have withdrawn the conference abstracts it presented in 1997 based on this data, or issued a public statement regarding the (alleged) violations later. The Apotex abstracts used the same LA-01 and LA-03 data as Dr. Olivieri, but claimed that the data demonstrated that L1 was effective and safe. If there were such extensive protocol violations, they should not have used the data. Instead, the company used such publications in a Priority Review Submission to Health Canada in September 1997.¹⁹

It is important to note that none of Dr. Olivieri, the patients in the two trials, the REB, or the administrations of the hospitals in which the trials were being conducted, were given any advance notice of the trial terminations and withdrawal of the drug supplies by Apotex. A critical fact is that Apotex warned Dr. Olivieri not to disclose any information about risks, to patients in particular.

It is a central fact of this case that both the long-term trial (LA-03) and the randomized trial (LA-01) were terminated and never reinstated. Under the contracts for the two trials, the company had the right to do so (see section

*We have not taken a position on the issue of whether or not there were protocol violations of such significance as to materially compromise the data of the Toronto trials, an issue presently before a court of the European Communities (see section 5U). The issue discussed here is the reason Apotex terminated the trials at the time it took this action.

5A), and it exercised this right. Dr. Spino confirmed this in a letter to Health Canada on January 28, 1997:

On May 24, 1996 Apotex notified the Bureau that that we had discontinued studies, code named LA-01 and LA-03, at the Hospital for Sick Children.²⁰

As noted in sections 5G and 5H, the fact that *both* trials had been terminated was clearly and repeatedly recorded in HSC records. Despite this documentation, HSC officials later put forward testimony to the contrary. Their incorrect testimony to the Naimark Review in 1998 and to the subsequent Medical Advisory Committee (MAC) investigation fueled and prolonged the L1 controversy. (See sections 5K, 5O, 5P and 5R.)

Conclusions

1 | We conclude that Apotex conducted itself inappropriately in the following ways:

- a. Apotex cancelled the trial because the investigator, on direction of her REB, was about to disclose the risk of loss of sustained efficacy to patients and others, as required by Canadian law and by national and international guidelines for research involving human subjects. Legal and ethical standards do not require that investigators be proven correct about their concerns—only that if and when in their opinion a significant risk has been identified, they must disclose that risk to the trial participants.²¹ Therefore, while Apotex had the right to terminate the trials, termination should not have been threatened or carried out because the investigator had identified a risk and planned to inform study participants.
- b. By warning Dr. Olivieri she would be subject to legal action if she disclosed this risk to patients and others with a right or need to know, Apotex violated her academic freedom and impeded her in the exercise of her ethical and administrative obligations.
- c. Apotex developed and disseminated *post hoc*, plainly self-serving rationalizations for terminating the trials that differed significantly from its own earlier statements as to why it terminated them.

2 | Even though Apotex's actions were inappropriate, it did have the right under the contracts, and also under the protocols, to terminate both trials at any time, for any reason. Therefore, after May 24, 1996, when Apotex unilaterally terminated the trials, the patients who had been enrolled in the LA-01 and LA-03 trials were no longer subjects of research. Consequently, they were no longer under the jurisdiction of the REB. Since Apotex had terminated both

trials and their corresponding protocols, there was no basis for any REB involvement in the subsequent management of care of these patients.

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5G | Post-termination events

(1) The new L1 treatment arrangement under EDR

THE ABRUPT TRIAL TERMINATIONS and legal warnings by Apotex on Friday, May 24, 1996 occurred with apparent disregard for the interests of the patients who had been enrolled in the trials. On May 25, Dr. Olivieri and Dr. Koren jointly wrote to Dr. Haslam, HSC Pediatrician-in-Chief and the University's Chair of Pediatrics, to advise him of this development, copying their letter to Dr. Arnold Aberman, Dean of the University's Faculty of Medicine, Dr. Michael Baker, Physician-in-Chief of TTH, and other HSC and TTH officials. Drs. Olivieri and Koren outlined events through 1995 and up to Apotex's actions of May 24, 1996, when:

[W]e received a letter terminating both studies, and written and phone messages indicating that legal action would be taken were we to breach confidentiality of either study. ...

While we have no way of knowing the motivation of Apotex at this time, this sequence of events has the appearance of a pharmaceutical company attempting to suppress data that could reasonably be expected to prompt regulatory agencies, once informed of this unexpected development, to request further investigation of this agent before licencing could be approved. ... [O]bservation of sustained efficacy of this agent, the use of which has potentially fatal adverse effects [ineffective iron chelation results in adverse effects of iron loading], would appear necessary before responsible development of the drug can continue. We have indicated this to the company on several occasions. Now that this contract has been prematurely terminated, we are uncertain of the responsibility on the part of Apotex to communicate these findings to regulatory agencies. Apotex has indicated, moreover, that it is a breach of confidentiality for us to do so ourselves. Finally, our patients will, under this instruction under *threat of legal action*, be terminated prematurely on the study without explanation provided to parents and families.

... Because *this series of events has ethical implications for the safety of patients*, both those in whom loss of efficacy has been observed, and all those who, in good faith, signed a consent and information form to complete this trial at the Hospital for Sick Children, *as well as to the Hospital itself and ourselves as researchers*, we will need your advice and guidance as to how to proceed.¹ (emphasis added)

Drs. Olivieri and Koren stated they would be seeking legal advice from the Canadian Medical Protective Association (CMPA).

We have no record of any response from Dr. Haslam. However, Dr. Baker suggested to Dr. Olivieri that Dean Aberman be approached for assistance. Dean Aberman met with Dr. Olivieri and her CMPA legal counsel, Mr. Joseph Colangelo on June 4, 1996. Dean Aberman agreed to their request that he "try to mediate the dispute between her and Apotex."² He had discussions with both parties and then convened a meeting on June 7, 1996 attended by Dr.

Olivieri, Dr. Koren, Dr. Brittenham, and Dr. Spino and other representatives of Apotex.³ Prominent among Dr. Olivieri's objectives for this meeting was reinstatement of the trials.⁴ Her reasons were twofold: so that the loss of response in some patients could be studied and the efficacy and safety of the drug further investigated; and so that patients who wished to continue on the drug and for whom it was considered sufficiently safe for them to continue, could continue.⁵ However, Apotex would not agree to reinstate the trials. Dean Aberman summarized the main result of the meeting as follows:

Although Apotex would not change their position on discontinuing the clinical trials, Apotex agreed to the Emergency Release of L1 to any patient who was on L1 during the trial, if requested by Gidi [Dr. Koren]. At the meeting, that was considered to be a satisfactory resolution of that issue.⁶ (emphasis added)

Thus, as a result of this June 7 agreement, those patients in the two former trial cohorts for whom it was considered sufficiently safe to continue on L1 would be allowed to continue on this treatment, as patients being administered an unproven drug by their treating physician, Dr. Olivieri, if, fully informed, they wished to continue. Dr. Koren's role in this arrangement was that of an intermediary in the drug supply,⁷ because "the relationship between Apotex and Nancy was beyond repair," Dean Aberman reported.⁸ This implies that the relationship between Apotex and Koren was good and indeed, as noted earlier, Apotex had the understanding that Dr. Koren supported its position that there was no risk of loss of sustained efficacy. Even though Dr. Koren co-signed the letter of May 25, 1996 outlining Dr. Olivieri's findings and the Apotex reaction, the company stated in writing (before and after May 25, 1996) that since February 1996 Dr. Koren disagreed with Dr. Olivieri and supported its position.⁹

The new arrangement was under the Emergency Drug Release (EDR) program of the Health Protection Branch (HPB) of Health Canada. This program provides for an arrangement among three parties: the practitioner (Dr. Olivieri), the manufacturer (Apotex) and the Director of HPB. The relevant provisions of the Canadian *Food and Drugs Act and Regulations*, as they apply to a "new drug," that is, a drug unproven as to safety or efficacy, are as follows:

C.08.010. (1) The Director may issue a letter of authorization authorizing the sale of a new drug for human... use to a practitioner... for use in the emergency treatment [EDR] of a patient under the care of that practitioner, if

...

(b) *the practitioner*¹⁰ has agreed to*

*The practitioner in this instance was Dr. Olivieri, the treating physician of the patients. It was not Dr. Koren, who later incorrectly claimed to be the practitioner for this EDR. (See endnote.)

(i) *report to the manufacturer of the new drug and to the Director on the results of the use of the new drug in the medical emergency, including information respecting any adverse drug reactions encountered, ...*¹¹ (emphasis added)

Under clinical ethical norms for physicians, Dr. Olivieri was also obligated to inform patients of any adverse drug reactions that might occur. Therefore, she had to continue to monitor patients, both because she had a legal and ethical obligation to them, and because she was legally required to report on the results of their treatment, including any adverse reactions, to Apotex and to HPB.

The new treatment arrangement did not require REB approval, because the patients were no longer in a clinical research trial. Nothing in the *Food and Drugs Act* and *Regulations* governing EDR, the MRC Guidelines on Research Involving Human Subjects, or the HSC policies in place at the time, required that treatment with a drug through EDR be subject to ethics review. Dr. Koren's own textbook on pediatric research ethics published in 1993 explicitly stated that in the Hospital for Sick Children, EDR drug treatment did not require approval of the REB.¹² Indeed, the REB was not involved in the meeting that resulted in the agreement on this arrangement—there was no requirement in policy or practice for it to be involved in an EDR arrangement.

(2) The issue of informing the regulators

A second issue discussed in Dean Aberman's mediation meeting was the matter of informing the regulatory agency, HPB, of the unexpected risk that had been identified. Dr. Aberman recorded that:

It was agreed that Nancy [Dr. Olivieri] and Apotex would go jointly to HPB.¹³

However, it is clear that not all parties had the same interpretation of this part of the discussion, because Apotex subsequently used legal warnings to deter Dr. Olivieri from any meeting with HPB, joint or otherwise, as we discuss later (section 5.H(2)).

(3) Continued Apotex support for Dr. Koren's research

Apotex's termination of the contracts and trials left uncertain the employment and training of three research fellows who had been engaged on term contracts to assist in the work of the L1 trials. An agreement was reached in Dean Aberman's June 7, 1996 mediation meeting, "to allow the postdoctoral fellows recruited for the trial to finish their training," as Dr. Koren later wrote.¹⁴ The research fellows were appointed in Dr. Koren's Division of Clinical Pharmacology and Toxicology, but during their work on

the trials they were jointly supervised by Dr. Olivieri and him. Two fellows received salary support from Apotex, and the other from the MRC grant for the LA-01 trial (see section 5A).

Although Apotex refused to reinstate the trials, there was substantial close-out work to be done in accordance with the protocols, along with data analysis for possible future publications. Apotex itself required close-out data for regulatory purposes. In addition, Dr. Koren was conducting a separate study, on the use of L1 in acute iron poisoning in an animal model, and it also was funded by Apotex.¹⁵ (Dr. Olivieri was not involved in the animal study.) It was agreed that the fellows would continue to be employed, and that their salary support would initially continue from the same sources as before the trial terminations. It was also agreed that, eventually, their supervision would be transferred over to Dr. Koren alone. To this end, “Dr. Koren, with Dr. Olivieri’s full knowledge and support, persuaded Apotex to continue to fund the fellowships.”¹⁶ Post-trial Apotex funds were deposited in Dr. Koren’s research accounts for salary support to the fellows. The investigators, Dr. Olivieri and Dr. Koren, agreed on an interim basis to continue some salary support for one of the fellows from the balance of the MRC grant for the LA-01 trial and a grant from the Cooley’s Anemia Foundation.¹⁷ Thus, the three research fellows continued in their programs, assisting with the close-outs of the clinical trials, in addition to other studies directed by Dr. Koren.

The total amount of funding provided by Apotex to Dr. Koren’s HSC accounts for research on L1—as a treatment for iron loading in thalassemia patients—was very substantial. In a letter to him in October 1997 requesting data, Dr. Spino stated:

As you are aware, Apotex is continuing our development efforts with deferiprone.... Given the extensive resources Apotex committed to the LA-01 and LA-03 trials (in excess of the \$1,000,000 paid to the Hospital for Sick Children), we are entitled to access to all data generated during these studies.¹⁸

Most of this funding went into accounts for which Dr. Koren had signing authority—the LA-01 contract specified that the Apotex funds for this trial would be deposited in his division in HSC (not Dr. Olivieri’s division), and on May 24, 1996 Apotex terminated all of its contracts with Dr. Olivieri and never subsequently provided research funding to her. Examination of the payment schedules in the LA-01 and LA-03 contracts, and a 1996 cumulative account statement for LA-01 indicates that approximately three-quarters of this total of \$1,000,000 was transferred to HSC accounts during the period 1993–1996, before the trials were terminated.¹⁹ We therefore conclude that, after the trials were terminated, approximately \$250,000 was transferred by Apotex to HSC accounts which supported Dr. Koren’s research.

There is a public record of a grant to Dr. Koren of \$250,000 in this time period. It was listed in 1999 on the website of the University’s Department of Pediatrics as received in 1995–1996 for use in 1996–1997. Unlike grant entries for all other members of Dr. Koren’s Division in the Department during that period, Dr. Koren’s entry does not specify the source or purpose—instead, this entry said “Industry/Miscellaneous.” In 2000, the University of Toronto Faculty Association was advised by the University that Apotex was the source of this \$250,000 grant to Dr. Koren.

(4) Lack of involvement by senior HSC administrators

Even though the actions of Apotex affected the interests of HSC patients, the rights of HSC staff physicians Dr. Olivieri and Dr. Koren, and the authority of the HSC Research Ethics Board, senior HSC administrators did not involve themselves in any effective way in the L1 dispute. Dean Aberman advised them of his meeting with Dr. Olivieri on June 4 and his mediation meeting on June 7, and of subsequent discussions that summer with Apotex in regard to its legal warnings to Dr. Olivieri.²⁰ An uncontroversial finding of the Naimark Review established by the HSC Board of Trustees in 1998 was that:

... the Hospital has interests and responsibilities in relation to clinical trials being conducted in the Hospital, even though it is neither a sponsor of the trials nor party to contracts between external sponsors and investigators. The interest of the Hospital is both general and particular.²¹

The Naimark Review provided a significant example of how the Hospital apparently failed to take steps to fulfil these responsibilities or defend its interests:

A detailed review of the Trials Contract and the protocols for the trials was apparently not carried out at the time the Executive was first alerted to non-renewal of the contract and the threats of legal action [May 25, 1996]. In retrospect, a detailed review would have been appropriate.²²

A detailed review might have noted the October 1995 contract for the LA-03 trial. This contract “supplanted” any previous agreement on the LA-03 trial. It had *no* confidentiality clause, so Apotex in actuality had no contractual basis with which to attempt to prevent Dr. Olivieri from communicating information about the risk she identified in LA-03 data in 1996 to anyone. The contract also specified that Apotex had the right to terminate the LA-03 trial. A detailed review of contracts and protocols should have included obtaining legal opinions on these documents. However, the Hospital apparently did not obtain a written legal opinion until October 1997, and that only on the LA-01 contract. That legal opinion did not fully address the issues at stake: it stated that a full answer would depend on “whether there were public policy concerns about information relating to public health and welfare.”²³ It is precisely “public

policy concerns” that have been at issue throughout this entire matter. (See section 5T.)

In 2000, Professor Emeritus and former Dean of Law (Queen’s University) D.A. Soberman gave an opinion to this committee of inquiry. We provided him with a copy of the LA-01 contract with its clause 7 on confidentiality. With reference to case law, as well as chapters from his own textbook and another textbook on contracts that offend public policy, and he wrote:

*To the extent that it prohibits a physician from disclosing to a patient information that the physician has acquired pursuant to her research (or otherwise), this clause is illegal and void if there is a material or significant risk to the patient.*²⁴

(Professor Soberman’s letter is reprinted in full as Appendix F. See also section 5T.)

The Naimark Review also found that:

By virtue of being an academic health sciences centre, the Hospital has a general interest in promoting academic freedom and free communication. There may be differing views about whether or not the Apotex-Olivieri case was the occasion upon which to publicly ‘take on Apotex’ on the issue of free communication. Certainly many scientists wish that had been done, not only for the sake of Dr. Olivieri, but also as a matter of principle.²⁵

The fact is that the Hospital did not “take on Apotex.” An example of an action that the Hospital could have taken when the legal warnings to Dr. Olivieri were first issued by Apotex in the summer of 1996, but which it did not take until early 1999, would have been to provide legal support backing up that provided by the CMPA. Following interventions by outside parties and the University of Toronto, the Hospital signed an agreement on January 25, 1999 that included the clause:

If Dr. Olivieri is required to defend herself in any legal action brought by Apotex arising out of facts which occurred prior to January 25, 1999 for which CMPA refuses to provide coverage, HSC will pay her costs of defending such an action. In the unlikely event that Apotex were successful, HSC agrees to indemnify Dr. Olivieri with respect to any award or judgment.²⁶

HSC could have offered such support in the summer of 1996. Had it done so, the course of events may well have been different.

In summary, the Hospital for Sick Children had opportunities to fulfil its responsibilities and defend its interests, but for more than two years it did not act. The Naimark Review said that some individual administrators made “personal representations” to Apotex.²⁷ It was quite clear from the fact that Apotex continued to issue legal warnings to Dr. Olivieri—none of which has yet been rescinded—that such “personal representations” were ineffective,

yet the weight of institutional authority and resources was not brought to bear to ensure effectiveness.

To our knowledge, no reason has been recorded by HSC administrators to account for their lack of involvement in the L1 controversy between May 1996 and February 1997, when a new element of the controversy prompted direct involvement by Dr. O’Brodivich. In particular, they apparently did not provide the Naimark Review with a reason. In consequence, the Naimark Report speculated:

This lull in interaction [between Dr. Olivieri and the HSC administration in the L1 controversy] may perhaps be explained by the fact that, in the last six months of 1996, Drs. Olivieri, Goldbloom and O’Brodivich were intensely involved in meetings and correspondence related to disagreements about the decentralization of the Sickle Cell Disease Program, and Dr. Olivieri’s role in that process.”²⁸

(See section 5M.)

Conclusions

1 | Apotex refused to reinstate the Toronto trials of its drug L1. Apotex agreed to reinstate the supply of L1 under a non-trial EDR treatment arrangement, as mediated by Dean Aberman. Dr. Olivieri was “the practitioner” under this arrangement. Therefore, after May 24, 1996, the patients who continued on L1 were no longer subjects in a research trial.

2 | The REB did not have jurisdiction over this EDR arrangement.

3 | Under this EDR arrangement, Dr. Olivieri had only three reporting obligations in the event of adverse drug reactions: to the patients, to Apotex and to the Health Protection Branch.

4 | Apotex provided very substantial research funds in support of Dr. Koren’s research programs, not only during the trials, but after the trials were terminated. He did not disclose the source of a \$250,000 research grant he received around the time of the trial terminations—much later, it was confirmed that the source was Apotex.

5 | Senior medical administrators did not effectively involve themselves in the dispute between Apotex and Dr. Olivieri, and offered no effective assistance to her during the first two and one half years. The Hospital did not take effective action to ensure that its responsibilities were fulfilled (until January 1999).

5H | Expanded disclosure

(1) Disclosure to patients

I. INFORMATION TO PATIENTS AND MONITORING UNDER EDR

DR. OLIVIERI WAS UNWILLING to administer L1 (the safety and efficacy of which had not been established, and for which a new risk had been identified—loss of sustained efficacy), unless the patients were informed of the risk, agreed to accept the risk, and also agreed to be monitored by the same efficacy and safety tests as in the protocols of the terminated trials. However, Apotex had specifically warned her not to inform patients—that she could face legal action should she do so.

CMPA legal counsel jointly represented Dr. Olivieri and Dr. Koren, since the latter also had received the initial legal warning from Apotex. Following the CMPA’s advice to minimize legal exposure, Dr. Olivieri maintained a record demonstrating that whenever she communicated information about L1, it was because she was complying with a legal obligation or other directive. Accordingly, in July 1996, after the re-supply of L1 had been arranged under EDR, she and Dr. Koren jointly wrote to Dr. Zlotkin, whose term as REB Chair had just expired, with a copy to his successor Dr. Aideen Moore. Dr. Olivieri thereby put on record that she was now going to implement a directive Dr. Zlotkin had issued to her when he was REB Chair, to inform patients of a risk of L1. She and Dr. Koren wrote:

As you know, it is of great concern that APOTEX abruptly terminated these studies without warning and that the company expects that the revised forms will not be shown to patients. Indeed, we were both separately cautioned that we were not to inform the patients of our interpretation of the data. We believe that for any patients who will continue to be treated with deferiprone—through any mechanism—as well as those in whom we are recommending the drug be stopped because of failing efficacy, it is important to disclose fully and fairly to patients and parents that we believe that deferiprone therapy is less efficacious than was previously conveyed to them. All patients will be asked to read and sign the revised consent and information forms even if they do not remain under treatment with deferiprone. Given the current situation, we believe that we are obliged to do so to provide full disclosure to our families.¹ (emphasis added)

In this July 15 letter, Drs. Olivieri and Koren also stated that patients wishing to continue to be treated with L1, as an alternative to standard therapy, would have to agree to undergo the same monitoring tests as in the protocols for the terminated trials, including “annual liver biopsy.” They explained that was because the tests specified in the protocols provided “the minimum amount of monitoring necessary to ensure patient safety on this

experimental chelator.”* As outlined in section 5G, monitoring was required under the EDR arrangement, as well as by clinical ethics.

Although REB approval was not required under EDR, that did not preclude investigators informing members of the REB. Such communication did not imply REB jurisdiction was agreed upon. These facts were given additional emphasis by the letter Drs. Olivieri and Koren wrote to Dr. Dougherty, the investigator at the small LA-01 trial site in Montréal (7 of the 66 patients), also on July 15, copies of which they enclosed with the letter sent to Dr. Zlotkin and copied to Dr. Moore on that date. This letter discussed only the LA-01 trial, since Dr. Dougherty had not been involved in the LA-03 trial. Drs. Olivieri and Koren confirmed to Dr. Dougherty that Apotex had terminated LA-01 at its main site in Toronto. They advised that, in consequence:

The 59 patients entered into this trial at the Hospital for Sick Children, Toronto site have therefore been withdrawn from the study.... In our capacity as investigators of LA-01, and as directed by our Hospital’s Research Ethics Board, it is our responsibility to request that you provide your Institutional Review (Ethics) Board with these [enclosed] revised [Information and Consent] forms and that you inform your board that study LA-01, as previously presented and approved by the Research Ethics Boards of both hospitals, is now terminated. Continuation of the seven patients [in a research study] at The Montréal Children’s Hospital in Montréal will require you to present a new protocol as well as new information and consent forms to your Hospital’s Research Ethics Board.² (emphasis added)

II. THE MISUNDERSTANDING OF DR. MOORE

It is now clear that Dr. Moore, who was new to the position of REB Chair, misunderstood the letters Drs. Olivieri and Koren sent to Dr. Zlotkin and her on July 15, 1996. In a handwritten note-to-file two days later, she wrote, “Enrolled patients will continue in study if showing efficacy.”³ Apparently she believed that because some patients would continue being administered the drug, they must also be continuing to be in a research trial (“study”) under REB jurisdiction. She apparently did not appreciate the significance of the statement that, “APOTEX... terminated these studies,” as the letter copied to her on July 15 noted. The REB was not involved in the June 7 agreement

*The importance of monitoring procedures, notably liver biopsy, as a guide to therapy for thalassemia patients was by this time established in the medical literature. See, for example, G. Angelucci *et al.*, *British Journal of Haematology*, 89 (1995) 757–761. Also, in February 1996 Drs. Olivieri and Brittenham sent a major review article on iron-chelation therapy in thalassemia that explained the importance of liver biopsy as a guide to therapy to the journal *Blood*. It was published February 1, 1997 (*Blood*, 89, 3, pp. 739–761). On March 7, 1995 Dr. Olivieri had written to Dr. Spino stating that the existing monitoring schedule for LA-03 represented the minimum level compatible with safety.

on the EDR arrangement (there was no requirement that it be involved). It is probable that she therefore did not appreciate that Apotex owned the rights to manufacture and sale of the drug, had terminated both trials, had removed all of the drug from the Hospital's pharmacy, had refused to reinstate any trial, and had only reinstated the supply of the drug later, under a *new and different*, non-research, treatment arrangement. Dr. Moore's note-to-file suggests also that she had not understood the LA-01 and LA-03 protocols. Evaluation of such protocols is the principal means by which the REB provides ethics review for trials. The protocols themselves gave Apotex the right to terminate the trials (hence also to de-activate the protocols), independently of the contracts, which also gave Apotex this right.

Although the July 15 letter from Dr. Olivieri and Dr. Koren to Dr. Zlotkin stated unequivocally that both trials had been terminated, some of their shorthand use of terms elsewhere in the letter could have been confusing to Dr. Moore. For instance, Dr. Olivieri and Dr. Koren used the phrase, "Both protocols will continue as before," as shorthand for the monitoring regimes for the non-trial EDR, which were to be the same as in the terminated trials, for safety reasons, as the full text of the letter explained. However, their letter to Dr. Dougherty made clear that Drs. Olivieri and Koren understood that the protocols had been terminated, and that any new study would require submission of a new protocol. Dr. Moore appears to have misunderstood this point, as well. No new protocol was ever submitted to restart either of the terminated L1 trials in Toronto, a fact that Dr. Moore *did* understand, as is clear from letters she wrote to Dr. O'Brodovich in 1997 and 1998.⁴ However, in these letters she erroneously stated that the (terminated) LA-03 trial continued under the original (terminated) protocol. In the same correspondence with Dr. O'Brodovich, Dr. Moore also erroneously said that some patients who had been in the LA-01 trial and who continued on L1 after May 1996 had somehow been enrolled in what she thought was a continued LA-03 trial, despite the fact that the two trial protocols were substantially different. (See also section 5K(7).)

Dr. Moore's misunderstanding of mid-July 1996 should have been cleared up two weeks later, when Dr. Olivieri and her division head in Hematology, Dr. Melvin Freedman, submitted official notification forms to the REB that both trials had been terminated (forms stamped as received by the REB on August 1, 1996).^{5*} Unfortunately, Dr. Moore appears not to have

*The notifications of termination to the REB were for the research studies, "Evaluation of Efficacy of the Oral Iron Chelator L1 in Removal of Hepatic Iron in Beta-Thalassemia Patients" (this was the official title of the original pilot study that continued and acquired the additional title "LA-03" in 1993, after Apotex became involved) and "Randomized Trial of Oral L1 and Subcutaneous DFO in Patients with Thalassemia Major" (also referred to as "LA-01"). The notifications both said "terminated" on "May 24, 1996" and were signed by Dr. Olivieri on July

understood this very explicit and unambiguous notification to the REB. As a result, the incorrect notions she continued to have were reflected in her correspondence and in REB records during her three-year term of office. Her mistake and resulting inaccurate testimony contributed to the misunderstandings of others, notably the Naimark Review panel and the Medical Advisory Committee. (See sections 5O and 5P).

It is documented that in the summer of 1996 senior administrators of both the Hospital and the University did not share Dr. Moore's misunderstanding, an important fact for later reference. For instance, Ms. Anne Marie Christian, Associate Director of the HSC Research Institute, wrote to Apotex's Chief Financial Officer on July 5, 1996:

I have received your letter about the clinical trials LA-01 and LA-03 which were terminated.⁶

As noted in section 5G(1), Dean Aberman put on record Apotex's refusal to change its position on terminating the trials. Apotex itself wrote to Dr. Moore on July 29, 1996 "to close out discussions on the LA-01/LA-03 trials."⁷

Conclusions

1 | Dr. Olivieri put clearly on the record that she would only continue to treat patients with L1 under EDR if they were informed of the recently identified risk and accepted the risk. In addition, they must agree to the same monitoring tests for safety they had previously agreed to when entering the LA-01 or LA-03 trial.

2 | The new REB Chair, Dr. Moore, did not understand the fact that both trials had been terminated.

(2) Informing the regulators

As noted in section 5E, Dr. Zlotkin had instructed Dr. Olivieri to inform patients, the Health Protection Branch (HPB), and physicians responsible for the clinical care of patients involved in the LA-03 study, of the unexpected risk she had identified. The subsequent Apotex statements had warned her not to communicate with anyone who was not a party to the L1 contract, without the written permission of Apotex. They specifically warned her not to communicate with patients and the HPB. Thus if she complied with the

20 and 21, 1996. Both were signed by Dr. Freedman on July 25, 1996 and both were marked as "Rec'd: Aug. 1" by the REB. The forms also listed the REB application numbers for each: 90/523 and 91/620, respectively, and the date of "Last Appr[oval]: 01/07/95" for each.

REB instructions to communicate the risk, she could be subject to legal action by Apotex. However, by late July she had informed patients and the relevant physicians.

The remaining aspect of this problem ostensibly seemed to have been resolved on June 7, through Dean Aberman's mediation. He reported that an outcome of his mediation meeting was an agreement that Dr. Olivieri and Apotex would "go jointly to HPB."⁸ However, Apotex apparently came away from the meeting with a different understanding about this than Dean Aberman. On the same day as the mediation meeting, Dr. Olivieri wrote to Apotex to advise that she was intending to send information on the risk to the HPB, including Apotex's view as set out in its extensive correspondence with the REB and herself from the preceding four months. In this letter, she advised Apotex that she had tentatively scheduled a meeting with HPB for June 14, and asked to be informed "if you intend to have a representative present."⁹ She asked to be informed if Apotex wished to provide any documents additional to the items she listed.

The meeting with HPB tentatively scheduled for June 14 did not occur, but on June 19 Dr. Olivieri forwarded to Apotex a number of copies of material containing data and conclusions on the loss of efficacy of L1, for distribution to all responsible physicians treating patients with L1 and their hospital REBS, and to the three regulatory agencies of the countries in which the three L1 trials had been initiated: HPB, FDA, and the Italian Ministry of Health.¹⁰ These packages included copies of the revised information and consent forms for participants in the Toronto trials. In a follow-up letter to Dr. Spino the next day, Dr. Olivieri stated that she "required" Apotex to forward the extra copies to the relevant physicians and agencies.¹¹ This extent of disclosure of the risk went beyond the specifications of the REB directive (listed in section 5E). While she could not "require" this, it was reasonable for Dr. Olivieri to ask this of Apotex because the risk needed be disclosed to physicians and patients in other countries. She was here following CMPA advice on minimizing her legal exposure, by providing multiple copies of the documents to Apotex and asking them to transmit them to the intended recipients. Apotex, as the manufacturer, had obligations to communicate about adverse findings on an experimental drug.¹²

In response to this letter, Ms. Katherine Kay, legal counsel for Apotex, wrote to Dr. Olivieri on June 24 and informed her that Apotex had "no obligation to satisfy your requests" to transmit the information to the regulators and others. Ms. Kay also stated that Dr. Olivieri had:

at various times, actually taken and indicated an intention to take various steps which would clearly represent a breach of the obligations of confi-

dentiality which bind you and may well give rise to other causes of action of Apotex against you.¹³

However, Ms. Kay did not categorically refuse Dr. Olivieri's request to have the copies of her report distributed. Ms. Kay continued:

Apotex is willing to pursue some form of resolution, but you must recognize that you do not have the ability to unilaterally dictate what steps the company is to take. Apotex will consider your letter and respond.¹⁴

This apparently left the question open for a period of time.

It is relevant to note here that Dr. Spino had advised Dr. Koren in his letter of April 18, 1996 (copied to Dr. Olivieri) that Apotex had already forwarded Dr. Olivieri's February 1996 report on loss of efficacy to all of the physicians treating patients at the other Apotex-sponsored trial sites (Montréal for LA-01, and Philadelphia and three sites in Italy for the short-term trial LA-02) so these physicians already had been informed of the new risk.¹⁵ These physicians had obligations to inform their own hospital REBs of risks. Dr. Spino later advised Dr. Zlotkin that all of these other investigators had responded to the effect that they did not consider Dr. Olivieri's report of sufficient concern to "warrant notification of their REBs," adding that in February 1996 Dr. Koren had expressed a similar view.¹⁶ These investigators did not have patients who had been taking L1 for a long period, and the adverse effect identified by Dr. Olivieri arose in the long-term trial cohort.¹⁷

Apotex's delay in responding definitively to Dr. Olivieri's letters of June 19 and 20 resulted in her not taking further steps until after Apotex's Expert Advisory Panel (EAP) was convened and had reported, on July 12-13, 1996. Apotex's position in correspondence since February was that no one should take any action until its EAP reported. The EAP report favoured Apotex's interpretation of the data on efficacy of L1.¹⁸ However, two of the four members of this panel later made public statements that cast serious doubt both on the EAP process and on its interpretation of the data.*

In August it became clear that Apotex opposed *any* presentation by Dr. Olivieri to HPB, whether in a meeting jointly with Apotex or otherwise. However, by early August Dr. Olivieri succeeded in persuading CMPA that it was in the public interest that she report to HPB, without the consent of Apotex, and CMPA agreed to provide legal coverage if she were sued. The position CMPA communicated to her in writing on August 7 was that, "such [disclosure to HPB] would be in compliance with statutory requirement."¹⁹ Accordingly, she arranged to meet with HPB on August 14 to present her

*See sections 5E (footnote), 5 I and 5L for published statements by EAP members Dr. Beatrix Wonke and Dr. Mary Corey. In a response to the EAP report written in August 1996, Drs. Olivieri and Brittenham said that the EAP had committed methodological and other errors.

findings on the risk of loss of efficacy of L1. The response of Apotex was to write on August 13 to HPB to suggest that it should not give any weight to Dr. Olivieri's findings, and to issue another legal warning to Dr. Olivieri on August 14, the day of her meeting with HPB.²⁰

In this August 14 legal warning, counsel for Apotex wrote to Dr. Olivieri's counsel concerning Dr. Olivieri's meeting that day with HPB saying that the proposed meeting was "inappropriate," and that:

Apotex has spoken with officials at the Health Protection Branch regarding the issues raised by Dr. Olivieri, and further details will be provided to HPB when Apotex's annual report is delivered, which is scheduled to take place before the end of August.... Apotex is growing increasingly concerned about the continued aggressive actions taken by Dr. Olivieri in attempting to malign the efficacy of Apotex's L1 in thalassemic patients, in spite of peer review which indicates that her allegations are incorrect. Unless this conduct ceases immediately, Apotex is prepared to take whatever legal steps are necessary in order to ensure that the conduct ceases and to obtain appropriate compensation for damages sustained.²¹

Despite these warnings from Apotex, Dr. Olivieri met with HPB on August 14, 1996 and informed the regulatory authority about her loss-of-efficacy findings.²² Apotex had a representative present, but not to present its view on the data.²³ Its position was outlined in its letter to HPB of August 13, which concluded:

The information, summarized above, will be included in greater depth in our Annual Report to HPB which is scheduled to arrive this month. We have informed Dr. Olivieri's lawyers that we see no useful purpose in her meeting with HPB.²⁴

Dr. Olivieri was accompanied to her meeting with HPB by Dr. Brittenham, and they asked for assurance that HPB would take steps to ensure that the authorities in other countries where L1 was in use would be advised, so that thalassemia patients outside Canada could know of the risk. HPB declined to provide such assurance. It was only after the refusal by HPB to take this responsibility that Dr. Olivieri succeeded in persuading CMPA to provide her with legal support to publish her findings in the scientific community, so that the information on the risk would reach physicians and patients outside Canada (see below).²⁵

(3) Informing the scientific community

By 1996 the drug L1 was in use in several countries, in addition to those where the Apotex-sponsored trials had been running. For instance, it was being administered as an experimental drug in England and Switzerland, and it had been licenced for therapeutic use in India. The best way to ensure that the

information about a medical risk becomes generally available is through scientific publication. This is one of the reasons why academic freedom—the right of university researchers to make their views and findings known—is very important. Dr. Olivieri wished to publish her findings, but Apotex continued to warn her that she would face legal action if she did. In this situation, her institutions, the University and the Hospital, had a responsibility to defend her academic freedom. Yet for more than two years neither the Hospital nor the University provided effective assistance.

Dean Aberman approached an Apotex official to advise the company to “stop threatening” Dr. Olivieri,²⁶ but his interventions were not effective—the series of written legal warnings continued, and he was copied on some of them. (See section 5N.) In regard to the Hospital Executive and the REB, there is no evidence that they provided any meaningful support to Dr. Olivieri in exercising her academic freedom. This is despite the fact that on July 17, 1996, Dr. Aileen Moore (then Chair of the HSC REB) made the following handwritten note-to-file, “Issue of being able to publish results of patients studied is an ethical one, and REB will support Dr. Olivieri.”²⁷

CMPA counsel Mr. Steven Mason arranged a meeting on July 18, 1996 with HSC Executive members Vice-President Dr. Alan Goldbloom and Pediatrician-in-Chief Dr. Hugh O’Brodivich, and Dr. Koren and Dr. Olivieri, in which the issue of scientific publication was discussed.²⁸ Dr. Koren indicated that he was in favour of publication as, in his view, physicians around the world were moving forward with the use of L1 because of the favorable results published in April 1995 in the *New England Journal of Medicine* by Drs. Olivieri, Brittenham and Koren.²⁹ In the meeting, Drs. Goldbloom and O’Brodivich agreed that researchers should be able to share their information with the scientific community even if there were conflicting viewpoints. They suggested that Dr. Olivieri forward a copy of her proposed abstracts for the December 1996 meeting of the American Society of Hematology (ASH) to Apotex, and invite Apotex to make its own submissions if it disagreed with her results. Dr. O’Brodivich’s notes on the discussion record that, “Alan & I recommend/support dual abstracts—Nancy—Apotex—to ASH,” that there was a “scientific controversy,” and that “HSC is not arbitrator of scientific discrepancies.”³⁰ It is not clear what Drs. O’Brodivich and Goldbloom meant by “support,” as no effective support for Dr. Olivieri’s academic freedom to publish abstracts or articles was provided by the HSC Executive (until early 1999 when others intervened).

The suggestion by Drs. Goldbloom and O’Brodivich that Apotex present its own abstract at the ASH meeting is of interest, in that none of the Apotex personnel who had been involved with the Toronto trials had the expertise to have an abstract accepted by the American Society of Hematology. Apotex

hired its first staff hematologist in mid-1996, Dr. Fernando Tricta, who had been involved with the LA-02 trial in Italy, but not with the Toronto trials. On November 26, 1996, only a week before the ASH meeting, he wrote to Dr. Olivieri asking her to persuade the program organizers to grant him standing to present the Apotex view.³¹ This request came after legal warnings to deter her from presenting her results at this meeting, together with written attacks on her scientific integrity, by his superior at Apotex, Dr. Spino (see section 5I). Dr. Tricta's request was followed a day later by another legal warning to Dr. Olivieri from Dr. Spino to deter her from speaking at ASH.³²

In late July 1996, Dr. Olivieri had prepared two draft abstracts for the ASH meeting, on data from the LA-01 and LA-03 trials.³³ The drafts were sent to Dr. Koren on July 30 for his comments and revisions.³⁴ The drafts were also sent to Apotex on August 1, 1996 for its consideration. Apotex responded on August 12, 1996, with another legal warning. It refused to consent to the submission of these abstracts for publication and concluded by saying:

Your unfounded allegations may have ramifications on *the commercial viability of this product* and, if that proves to be the case, Apotex would be compelled to take appropriate action.³⁵ (emphasis added)

However, by mid-August, Dr. Olivieri had succeeded in persuading CMPA to provide her with legal coverage to publish her findings in the event Apotex sued or sought an injunction to prevent her from doing so. She was assisted in this by Professor Sir David Weatherall of Oxford and Dr. David Nathan of Harvard,* who had spoken with her CMPA counsel Mr. Mason. They outlined for him the “reasons why publication is so important.”³⁶ Mr. Mason conveyed these reasons to senior counsel in his law firm and to officers of the CMPA, adding:

The experts feel that Dr. Olivieri must publish her findings immediately. The next major meeting is in December in Orlando (ASH). The deadline for submissions is August 22, 1996.³⁷

After her August 14 meeting with HPB in Ottawa, Dr. Olivieri met with CMPA officers and reported that HPB had declined to assure her that they would advise regulatory agencies in other countries where L1 was in use, of the risk she had identified. She added that this made publication in the scientific community all the more urgent. Following this meeting, her CMPA counsel wrote to advise Apotex that Drs. Olivieri and Koren both believed that the data contained in the abstracts were correct, and that the matter of disclosure of this information was important not only to the members of the scientific community but to

*Sir David Weatherall, FRS: Regius Professor of Medicine and Director of the Laboratory of Molecular Medicine, University of Oxford. Dr. David Nathan: President of the Dana-Farber Cancer Institute, Professor of Pediatrics, Harvard University and former Physician-in-Chief of Children's Hospital, Boston.

thalassemia patients as well. In this letter of August 19, 1996, her counsel further advised Apotex that while Dr. Olivieri sought their approval for the abstract submissions, she would nevertheless submit the abstracts for publication without the approval of Apotex, as:

there is an overriding public interest in the publication of the data and this must override any duty of confidentiality which Apotex claims Dr. Olivieri owes to it.³⁸

On August 19, Dr. Olivieri sent copies of her two abstracts to Apotex in final, revised form. She advised that she would be submitting them to ASH on August 22, and closed her letter by saying, "I trust you will provide a favourable response to the enclosed revised abstracts."³⁹ Apotex responded three days later with a strongly worded letter, accusing her of improperly manipulating data in both abstracts, and issuing another legal warning to deter her from submitting them to ASH.⁴⁰ This August 22 letter was copied to Dr. Goldbloom, as well as to Dean Aberman. Dr. Olivieri replied the next day, rejecting the accusations and explaining that the data had been properly recorded and analysed.⁴¹ On that day, August 23, counsel for Apotex issued another legal warning.⁴² Despite the legal warnings, Dr. Olivieri submitted her abstracts to ASH, with CMPA legal support.

Meanwhile, Dr. Koren had reviewed the abstracts and faxed suggested minor revisions to Dr. Olivieri. He did not disagree with her findings about loss of efficacy and Dr. Olivieri made wording changes in accordance with his suggestions. In mid-August 1996, however, Dr. Koren crossed out his name on a revised abstract and returned a copy to her indicating this.⁴³ In a subsequent telephone discussion involving Dr. Olivieri and their two CMPA counsel, Mr. Colangelo and Mr. Mason, Dr. Koren gave assurances that, in declining co-authorship, he was not signifying lack of support for Dr. Olivieri's findings. He said that he continued to support these findings, but that he had other difficulties and was not in a position to confront Apotex in a lawsuit.⁴⁴ It was not until seven months later, in March 1997, that Dr. Olivieri learned (through their joint CMPA counsel) that Dr. Koren had co-authored abstracts with Apotex employee Dr. Tricta for an April 1997 conference in Malta, that concluded that L1 was effective and safe.⁴⁵ The findings in these abstracts were in substantial conflict with the findings in her December 1996 ASH abstracts that Dr. Koren had assured her and their joint CMPA counsel he supported.⁴⁶

On November 27, 1996, a few days before the ASH meeting was to begin, Dr. Spino issued another legal warning to deter Dr. Olivieri from presenting her results. He again made accusations about discrepancies in data, as he had in August. In this letter he said that Apotex "cannot support your interpretation nor approve of your presentation," and:

by making your presentation without the consent of Apotex, you are in violation of your contract and confidentiality obligations to the Company.⁴⁷

Conclusions

1 | Dr. Olivieri advised HPB in August 1996 of the risk she had identified, thus complying with the HSC REB directive. She did this in the face of legal warnings by Apotex, after being assured of legal support by CMPA. She received no effective support in doing this from the Hospital, even though it was the Hospital's REB that had issued the directive. The agreement Dean Aberman had understood he had mediated, that Dr. Olivieri and Apotex would jointly meet with HPB to present their findings, did not result in a joint presentation meeting.

2 | Dr. Olivieri submitted two abstracts to ASH in August 1996. She did this with the legal support of CMPA, in the face of legal warnings by Apotex. Although the Hospital told her it "supported" submission of abstracts to ASH, she received no effective support from the Hospital. Dean Aberman's efforts to persuade Apotex to "stop threatening" her with legal action were clearly ineffective—the "threats" continued after his interventions, and he was copied on several of these.

3 | Apotex acted inappropriately in repeatedly warning Dr. Olivieri of legal consequences if she carried out actions that were required of her by the HSC REB, and by legal and ethical guidelines for research involving humans. It also violated her academic freedom in attempting to deter her from publishing scientific findings.

(4) Dr. Olivieri's 1996 abstracts

The two abstracts Dr. Olivieri submitted to ASH on August 22, 1996, and later presented during the ASH meeting in Orlando December 6-10, 1996, were on data from the long-term trial (LA-03) and the randomized trial (LA-01). The former were not subject to any confidentiality agreement, but the latter were subject to a one-year, post-termination publication ban (see sections 5A(3) and (4)). Dr. Olivieri's CMPA counsel had advanced the public interest defence for publication of both abstracts in their letter to Apotex counsel of August 19, 1996.⁴⁸ The CMPA counsel did not advance the additional argument in defence of publication of LA-03 data—that Apotex had no contractual basis on which to try to suppress this data. (We have not been able to ascertain why this argument was not advanced—see section 5T.)

The abstract on LA-03 data reported results for eighteen patients who had been enrolled for periods of time long enough for analysis of efficacy.⁴⁹ It was similar in form to Dr. Olivieri's report to the REB earlier that year, with patients grouped in various risk categories depending on hepatic iron concentration (HIC), and a graph indicating loss of sustained efficacy in some patients. The abstract on LA-01 data reported results for twenty-six patients (eleven on standard therapy, DFO, and fifteen on L1) who had been enrolled in that trial for at least two years.⁵⁰ The conclusion was that L1 was less effective than DFO to a statistically significant extent. In the course of her talk at the December ASH meeting, Dr. Olivieri noted that, "Both these trials were terminated prematurely by their corporate sponsor, the generic drug company Apotex, in May of this year."⁵¹

Drs. Olivieri and Brittenham cited and summarized these abstracts in their review article in the February 1, 1997 issue of *Blood*, in a Note Added in Proof.⁵² In this article they stated that both the long term trial (LA-03) and the randomized trial (LA-01) were "terminated" by the sponsor "Apotex Pharmaceuticals in May 1996."⁵³

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51 | Ongoing legal warnings

(1) The series of legal warnings by Apotex in 1996 and 1997

IN RESPONSE TO EACH of Dr. Olivieri's proposals to disclose information to patients, regulatory agencies, and the scientific community, Apotex issued legal warnings to deter her. These began on May 24, 1996, the day Apotex terminated the LA-01 and LA-03 trials in Toronto and Dr. Olivieri's LA-02 consulting contract. One of the warnings on that date stated:

... *all* information whether written or not, obtained or generated by the Investigators during the period of the LA01 contract and for a period of one year thereafter, shall be and remain secret and confidential and shall not be disclosed in any manner to any third party except with the prior written consent of Apotex.... Apotex will... pursue all legal remedies in the event that there is a breach of these obligations.¹ (emphasis in original)

The series of warnings continued through May of the next year, at an average rate of approximately one warning letter per month to Dr. Olivieri or her legal counsel, written either by Dr. Spino or Apotex's legal counsel. None of these warnings has ever been rescinded. In this section we review the series of warnings subsequent to the first three issued in May 1996 (see section 5F).

A legal warning dated June 24 and another dated August 14 were intended to deter Dr. Olivieri from informing the regulators of the risk of L1 she had identified. Two others, dated August 12 and 22 were intended to deter her from submitting her abstracts for the December ASH meeting, and another, dated August 23 warned of legal consequences if she communicated her findings to anyone.² An example of wording is in the August 12 letter from Dr. Spino:

We are particularly concerned that you continue to allege that there is lack of response to L1, in spite of scientific review to the contrary. Your unfounded allegations may have ramifications on the commercial viability of this product and, if that proves to be the case, Apotex would be compelled to take appropriate action.³

Similar wording is contained in a later warning, dated November 27, 1996, again to deter her from presenting her findings at the ASH meeting.⁴

Some of the warning letters refer to the July 1996 report of Apotex's Expert Advisory Panel (EAP), directly or through use of the term "peer review." For instance the August 14 letter by Apotex counsel said:

Given the conclusions of the Expert Advisory Panel, to suggest that this is a patient safety matter is simply incorrect.... As you can well understand, Apotex is growing increasingly concerned about the continued aggressive actions taken by Dr. Olivieri in attempting to malign the efficacy of Apotex's L1 in thalassemia patients, in spite of peer scientific review which indicates that

her allegations are incorrect. Unless this conduct ceases immediately, Apotex is prepared to take whatever legal steps are necessary in order to ensure that the conduct ceases and to obtain appropriate compensation for damages sustained.⁵

With regard to the references to the EAP report as “peer review,” it is relevant to note that all four panelists were selected and paid for their work on the panel by Apotex, and two of the four members of this panel subsequently made statements which cast serious doubt on both the process and the report of the EAP (see footnote here and section 5L).*

On May 24, 1996, Apotex had terminated Dr. Olivieri’s consulting contract for the LA-02 and issued a legal warning in regard to information from that trial. On November 7, 1996, Dr. Spino wrote to Dr. Olivieri to advise her that she was no longer a member of the LA-02 Steering Committee and to issue another warning. The letter said:

As you know, Apotex has made every effort to maintain a professional relationship with you.... Notwithstanding these efforts by Apotex, you have breached your contractual obligations to Apotex. In these circumstances, and after reviewing the matter with legal counsel, Apotex has no alternative but to advise that you are no longer a member of the LA-02 Steering Committee.... Furthermore, may I remind you that any information pertaining to Apotex-sponsored L1 studies which you may have obtained, whether from Apotex or others, remains confidential proprietary information of Apotex.⁶

As we discuss in section 5.K, in early February 1997, Drs. Olivieri and Brittenham and liver pathologist Dr. Ross Cameron identified a new and more serious risk of L1, namely, progression of liver fibrosis. This was a result of a review of serial biopsy slides in charts of patients in the former long-term (LA-03) trial cohort. On February 4, 1997 Dr. Olivieri informed

*One of the EAP members, Dr. Beatrice Wonke, was a member of a research team in England which had conducted a long-term study of L1. Later in the same year, she was co-author of an abstract at the December 1996 ASH meeting which independently reported findings of loss of sustained efficacy similar to those Dr. Olivieri reported at that meeting. Dr. Wonke’s ASH abstract expressed the same conclusion from her long-term study as Dr. Olivieri had from her LA-03 study, namely, “We conclude that long-term iron chelation with L1 alone is successful at maintaining body iron at a ‘safe’ level in only a minority of transfusion dependent patients.” (Abstract # 2592 in supplement to *Blood*, December 1996). In an article on the same study published in *Blood* in 1998, Dr. Wonke and her co-authors wrote, “Among the 17 patients tested, after a mean of 40 months of therapy (range, 27 to 49 months) only 2 showed liver iron levels [HIC] below 7 mg/g, a level considered safe, while 8 had levels above 15 mg/g, levels at which liver and cardiac damage are likely to occur.” (Article in *Blood*, 91,1 (1998), page 298.)

In August 1998, another EAP member, Dr. Mary Corey, stated in a letter to Dr. Manuel Buchwald, Director of the HSC Research Institute, as well as to the *Toronto Globe and Mail* (August 14, 1998) that the EAP had not been accurately informed as to the facts and circumstances by Apotex. For instance, Dr. Corey said to the newspaper, “we [the EAP] did not have the up-to-date data.” Dr. Corey confirmed and elaborated on her concerns in testimony to this Committee in 1999. (See section 5L.)

patients, and she informed Apotex by copy of a report she intended to send to the regulatory authorities in the USA, Canada, Italy and India. Apotex responded with letter February 11, 1997 which its legal counsel sent counsel for Dr. Olivieri warning her not to communicate her findings of this risk to anyone. The letter disputed that the finding could be correct, and said that:

The publication of the information she has generated, even if it is incorrect, would have a devastating effect on the development of L1. If L1 does enhance the rate of fibrosis development in thalassemic patients, this should be made known. On the other hand if it does not, it would be a travesty to frighten patients and their doctors with this mis-information. Dr. Olivieri's publication of this information will have serious and irreparable repercussions both in terms of health care and business.⁷

This letter said that Apotex had “grave concerns about the lack of scientific validity of Dr. Olivieri’s study” and “request[ed] that Dr. Olivieri refrain from sending” her report to the regulators, “until such time as Apotex has had an opportunity to appoint an independent hepatologist to review the slides from which Dr. Olivieri’s report was generated.”⁸ It warned that if the hepatologist to be appointed by Apotex did not agree with Dr. Olivieri’s finding, “Apotex will contest the right of your client to publish the information in light of her obligations of confidentiality under various contracts.”⁹ Thus, as with identification of the first unexpected risk of L1, Apotex’s position was that if it, or a person appointed by it, did not agree that there was a risk, then Dr. Olivieri could be subject to legal action should she disclose the risk to anyone. However, with CIPA legal support, she sent the report to the regulators on February 24, in compliance with her legal obligation as the “practitioner”¹⁰ under the EDR arrangement with Health Canada.

The February 11 warning letter requested in addition that Drs. Olivieri, Brittenham and Cameron withdraw an abstract they had submitted to the “Biomedicine ‘97” conference scheduled for late April in Washington. During February and March there were further communications among lawyers, with Apotex warning it would take legal action unless Dr. Olivieri withdrew abstracts sent to two other conferences (“HIV and Iron,” scheduled for mid-March in Brugge, and the “6th International Conference on Thalassemia and the Hemoglobinopathies,” scheduled for April 6–10 in Malta). In response to these warnings, Dr. Olivieri withdrew the Washington and Malta abstracts. She also withdrew as an author of the Brugge abstract, leaving her co-author Dr. Brittenham to present it.¹¹ Apotex then tried to persuade (as distinct from warning him of legal consequences) Dr. Brittenham not to present the Brugge

abstract.* Dr. Brittenham replied that it was important to present the abstract at a conference in Europe because:

[H]undreds of patients in Europe continue to be treated with deferiprone because of lack of knowledge of this unforeseen complication of therapy.¹²

Shortly before the Malta conference was to begin, Dr. Olivieri obtained copies of two abstracts that were to be presented there, co-authored by Apotex employee Dr. Tricta, Dr. Koren and others. These abstracts concluded that L1 was effective and safe. They used LA-01 and LA-03 data generated by Dr. Olivieri and Dr. Brittenham, without their knowledge or consent and without acknowledging their contributions. The abstracts made no mention of the risk of progression of liver fibrosis. Upon reading these, Dr. Olivieri re-submitted her previously withdrawn abstract to the Malta conference, this time with CMPA support. On April 3, 1997, Apotex's counsel wrote to Dr. Olivieri's counsel:

Apotex Inc. has stated on many occasions that Dr. Olivieri is not entitled to publish any such information without its consent... please note that Apotex will hold Dr. Olivieri liable for damages caused by unfounded statements about deferiprone at this [Malta] conference and others."¹³

Despite the renewed warning, Dr. Olivieri presented her findings a few days later at the meeting in Malta. Her report alerted clinical researchers administering L1 in other centres and a least one group, based in Switzerland, then took clinical measures to assess their patients for this previously unreported risk. (See section 5Q.)

Further legal warnings were issued to Dr. Olivieri in May 1997. On May 8, Apotex counsel wrote:

I would strongly urge you to caution your client against making any rash statements about L1.** Apotex will hold Dr. Olivieri responsible for any damages caused by unfounded statements about L1."¹⁴

On May 26, Apotex legal counsel wrote about a presentation regarding L1 that Dr. Olivieri was planning to make at the "Seventh Cooley's Anemia Symposium" in Cambridge, Massachusetts in June, saying:

To make such a presentation without the prior written consent of Apotex is a breach of Dr. Olivieri's contractual obligations.... your client is advised to

*The only contract Apotex had with Dr. Brittenham was his LA-02 consulting contract, so the company had no basis on which to issue legal warnings to him in regard to these conference abstracts.

**In his May 8, 1996 letter, Apotex counsel Mr. David Brown indicated that by "rash statements," he meant: i) the question for investigation raised by Dr. Olivieri at the December 1996 ASH meeting (whether a finding that an iron chelator chemically similar to L1 had caused progression of liver fibrosis in an animal model might mean that L1 could cause this adverse effect); and ii) the report by Drs. Olivieri, Brittenham and Cameron of early February 1997 concluding that L1 was the probable cause of progression of liver fibrosis in some patients.

refrain from continuing to mislead both the scientific and patient communities regarding her impressions that deferiprone exacerbates hepatic fibrosis. To present unsupported allegations at the meeting next week in Cambridge would cause damage to Apotex, for which Dr. Olivieri will be held responsible.¹⁵

The letter of May 26, 1997 appears to have been the last in the series of Apotex legal warnings, possibly because the one-year post-termination publication ban in the LA-01 contract had expired on May 24, 1997. However, none of the warnings has been rescinded, and in its “Statement of Defence and Counterclaim” filed in Ontario Superior Court on June 19, 2000, in response to the libel suit initiated by Dr. Olivieri, Apotex stated that it “pleads and relies on... provisions of the LA-01 Contract,” including “Clause 7” on confidentiality (see below).¹⁶

(2) Denials by Apotex

In 1998 and 1999 Apotex denied that it had ever advised, told, warned or threatened Dr. Olivieri in regard to communicating information about its drug L1. It made these denials both in connection with the risk of L1 Dr. Olivieri identified in 1996, loss of sustained efficacy, and in connection with the risk she identified in 1997, progression of liver fibrosis.* In a letter dated November 24, 1998 from Dr. Spino to the Naimark Review, Dr. Spino stated:

It is evident... that there was no threat to Dr. Olivieri relating to the presentation of information on hepatic fibrosis.

Dr. Spino concluded the letter by saying:

Apotex did not threaten Dr. Olivieri, and did not advise her not to tell patients or the REB about her alleged findings on deferiprone-exacerbated hepatic fibrosis.¹⁷

As we discuss in section 5.O, the Naimark Review panel apparently did not have access to a number of important documents, including some of the Apotex legal warning letters quoted above, and believed these statements by Dr. Spino.

On December 19, 1999, Dr. Barry Sherman, CEO and Chair of the Board of Apotex Inc. was interviewed by Leslie Stahl for the CBS television program *60 Minutes*. In this interview, Dr. Sherman denied that Apotex had told Dr. Olivieri not to tell her patients about her concerns about L1 effectiveness in some patients. The following is an excerpt from the transcript:

*The identification of the risk of progression of liver fibrosis is discussed in section 5K of this report.

Mr. SHERMAN: At no time was she told by anyone not to say whatever she thought was appropriate to any patient.

STAHL: We went to her colleague, Dr. Gary Brittenham, and he told us that he was in the room with her when a senior vice president from Apotex told them both not to tell the patients.

Mr. SHERMAN: Well, i— it's not true.

STAHL: And we have a letter.

Mr. SHERMAN: OK, let's see.

....

STAHL: (Voiceover) We showed him a letter from Apotex vice president Mike Spino. (footage showing the letter to Dr. Brittenham with excerpt highlighted: "Since we did not concur with her assessment of the drug's effectiveness, we could not allow such information to be transmitted to patients.") And we asked him about a message Dr. Olivieri says that same Mike Spino left on her answering machine.

Dr. Olivieri tells us that she has a phone message ...

Mr. SHERMAN: Yes

STAHL: ... from Dr. Michael Spino, in which he clearly states that she is not to tell her patients.

Mr. SHERMAN: Well, I—I—I don't believe that, because she says it is, because we've seen ...

....

Mr. SHERMAN: ... statement after statement [by Dr. Olivieri] is false¹⁸

The *60 minutes* program then broadcast excerpts from the recording of Dr. Spino's telephoned warning to Dr. Olivieri of May 24, 1996 (quoted in full in section 5F), including his statement:

... [I]f you in any way attempt to convey it [information that L1 had lost efficacy in a majority of LA-03 patients] you will be subject to legal action.

It is remarkable that officers of Apotex would make such statements in the face of the extensive documentary evidence of ongoing legal intimidation, in which Dr. Spino and Apotex lawyers repeatedly warned Dr. Olivieri about legal consequences should she fulfil her obligations to disclose risks to patients and others with a right or need to know.

The statements by Dr. Sherman quoted above and other statements by him broadcast on the CBS program resulted in a libel action initiated by Dr. Olivieri in Ontario Superior Court in 2000. In its "Statement of Defence and Counterclaim," Apotex asked for \$10 million in damages because of statements Dr. Olivieri had made concerning L1 and Apotex. In its counterclaim, Apotex cited a number of public statements Dr. Olivieri had made as evidence of alleged "injurious falsehoods against deferiprone" and claimed that she had made these with alleged "reckless disregard for their truth or falsity."¹⁹ It is of

note that one of the cited statements, made in December 1998, was Dr. Olivieri's response to a question, "What did you publish in the *New England Journal of Medicine*?" which was:

that 36% of patients treated with this drug [L1] long term had progression of liver damage and that in a substantial proportion of patients the iron levels during the treatment exceed the threshold for heart disease so its ineffective... and... toxic.²⁰

Dr. Olivieri's article in the *New England Journal of Medicine (NEJM)* was published in August 1998, more than a year after the publication ban in the LA-01 contract expired, yet Apotex stated in its counterclaim that it relied on this contract. Thus the fact that Apotex never rescinded any of the legal warnings is significant.

NEJM is a journal with rigorous refereeing standards. That repetition of information previously published in a refereed journal (and which has not been proven by scientific means to be wrong) would be cited as grounds for damages, should be a matter of concern to the academic community and to the wider public.

Conclusions

1 | Apotex denied that it warned Dr. Olivieri with legal consequences if she informed patients or others with a right or need to know of risks of L1. This was not true—it is documented that Apotex repeatedly warned Dr. Olivieri of legal consequences if she informed patients or others with a right or need to know of risks of L1.

2 | To a significant extent, Apotex’s legal warnings were effective. In a number of instances they resulted in modifying Dr. Olivieri’s behaviour. For instance, on CMPA legal advice she withdrew abstracts submitted to scientific meetings, and she delayed informing the Health Protection Branch of the risks she had identified until after she had informed Apotex.

5J | Trial close-outs & another stoppage in supply of L1

(1) Close-out patient assessments and data collection

The protocols for the trials required what is termed “close-out” work, that is, data collection necessary following trial termination or withdrawal of patients from an ongoing trial. For instance, the LA-01 trial specified:

On an annual basis or on study termination (completion of protocol or withdrawal), subjects will undergo additional safety and efficacy assessment. The following tests would be used ... : Liver biopsy, SQUIDS, Magnetic Resonance Imaging¹

The close-out work extended over a period of several months following the terminations in May 1996, and there is correspondence among Dr. Olivieri, Dr. Koren and Apotex during this period, discussing close-out assessments of patients and the resulting data being provided to Apotex.² The close-out work was completed by the end of October 1996.³ Dr. Olivieri wrote to Dr. Spino on November 15, 1996 advising that she would be presenting close-out data (along with earlier data) from the two trials at the ASH meeting in December. She enclosed for his information tables of data from the LA-01 and LA-03 trials, both data that had earlier been “recorded in the APOTEX baseline booklets” and data “recorded in the APOTEX close-out booklets.”⁴

Conclusion

Close-outs of both the LA-01 and LA-03 trials occurred, and this fact provides additional, independent confirmation that both trials had been terminated.

(2) Continuation of treatment of some patients under EDR

The LA-01 and LA-03 clinical trials were terminated by Apotex in May 1996. The REB was advised in writing in July by Dr. Olivieri, Dr. Koren and Dr. Freedman (Chief of Hematology) that both studies had been terminated by the sponsor and that the protocols were no longer active.⁵ Neither Dr. Olivieri nor Dr. Koren submitted any further protocols with respect to the use of deferiprone in the treatment of persons with thalassemia to the REB. Therefore, from the time the studies were terminated by Apotex, there were no thalassemia deferiprone protocols under the jurisdiction of the REB.

As a result of Dean Aberman’s meeting in June 1996, Apotex agreed to reinstate the supply of L1 through the EDR program of the federal government.⁶ Dr. Olivieri agreed to continue to treat patients with L1 under EDR only if the following conditions were met: that in their individual cases it was sufficiently

safe for them to continue on the drug; that they (or their families) read the revised information forms she had prepared describing the new risk of loss of sustained efficacy; that they (or their families) agreed to accept the new risk; and that they (or their families) agreed to monitoring with the same tests as specified under the protocols of the terminated trials, to ensure their safety. Consequently, there was a seamless transition in the monitoring regime from the trials to the subsequent EDR arrangement. Since these patients were not participating in a research trial and the tests were being conducted for patient care, not research purposes, it was not necessary for Dr. Olivieri to submit a protocol to the REB for tests conducted after May 1996. None of these tests was controversial in HSC in 1996 or in 1997.*

(3) The second stoppage by Apotex of the supply of L1

In mid-fall 1996, Apotex again stopped the supply of L1 (as it had in May, when it terminated the trials). On October 28, 1996, Dr. Olivieri wrote to Dr. Koren (copied to Dean Aberman):

I am told by Naomi Klein, our data manager... that we have not received a further supply of deferiprone for the patients at The Hospital for Sick Children previously enrolled on studies of LA-01 and LA-03, prematurely terminated by APOTEX in May, 1996. I am told by Naomi that Dr. M. Spino of APOTEX is now not willing to continue these patients on APOTEX L1 as he is concerned, I am told, that I will analyze and report this data, even if unfavourable. This is of concern to me because... we had received assurance from Dr. Spino in the presence of Dr. Arnold Aberman on June 6, 1996 [sic—June 7] that Dr. Spino, having supported enrollment of patients in these trials as recently as September 1995, and then prematurely terminated the trials, remained prepared to supply drug to all patients under compassionate use [EDR]. ... the failure to honour this agreement is of concern to the patients and to myself. Could we perhaps meet to determine the most satisfactory solution to this problem?⁷

Dr. Olivieri's letter raised several matters:

- the stoppage by Apotex in the supply of L1;
- the apparent refusal by Apotex to continue with the agreement mediated by Dean Aberman on June 7, 1996;
- the apparent disregard by Apotex for the interests and concerns of patients; and
- a possible reason for the stoppage.

*It was not until much later, during the proceedings of the Medical Advisory Committee (MAC), that one of the tests, liver biopsy, was questioned by Dr. Koren and Dr. O'Brodovich (neither of them expert in the treatment of thalassemia), who made incorrect statements to the MAC that liver biopsy was research, and was a risky procedure (see sections 5P and 5Q).

It appears that Dr. Olivieri's concerns were conveyed to Dr. Spino, as three days later he wrote to HSC Vice-President Dr. Goldbloom, requesting a meeting with Drs. Goldbloom, Koren, Freedman (HSC Chief of Hematology) and Aberman.⁸ The requested meeting was held on November 13, 1996. Dr. Goldbloom's notes on the meeting recorded:

The goal of the meeting was to find a way for Apotex to continue to provide L1 to patients who need and benefit from it, given that the working relationship between Dr. Nancy Olivieri and Apotex has not been mutually satisfactory. After discussion, it was agreed that a realistic option would be to provide medication under the Emergency Drug Release Program to Dr. Gideon Koren, in his role as Head of the Division of Clinical Pharmacology. Under this proposal, through collaborative arrangement between Haematology and Clinical Pharmacology... it was expected that a satisfactory and responsible process for providing needed medication to patients could be arranged. Details were left with Drs. Freedman and Koren to work out.⁹

This agreement appears similar to the one mediated by Dean Aberman in June, except that an additional intermediary, Dr. Freedman, Dr. Olivieri's Division Chief, was now to be included along with Dr. Koren. The strained relations between Dr. Olivieri and Apotex may have been one factor in the stoppage in the supply of the drug by Apotex, as Dr. Goldbloom reported. However, this cannot have been the only factor, because the new, November 13th arrangement did not resolve the supply issue, as is clear from the documentary record of subsequent weeks.

By all accounts, Dr. Koren had good relations with Apotex throughout the entire period of the L1 controversy, including 1996–1997. Nevertheless, he was not successful in getting the supply of L1 reinstated by the company. More than a week after the new arrangement had apparently been agreed upon, on November 22, 1997, Ms. Klein wrote to Dr. Koren (copied to Dean Aberman), telling him that some patients had “completely run out of the drug,” and that Apotex had not responded to her requests.¹⁰ Dr. Koren then wrote to Apotex on November 25 (copied to Dr. Freedman):

More and more parents are reporting not having any L1 left.... They are becoming inpatient [sic] and upset. Could you please advise me on what approach I should take in answering these parents. Naturally, the problem is of immediate urgency.¹¹

Dr. Koren's appeal was not successful, so Dr. Olivieri herself wrote to Apotex on December 2 concerning the supply of L1.¹² A month later, on January 8, 1997, she wrote to the concerned parent of a patient (copied to Drs. Goldbloom, O'Brodovich and Aberman), saying, “As you know, we await supply of this drug under Emergency Drug Release through APOTEX pharmaceuticals.”¹³ It appears that Apotex eventually supplied some quantities of L1,

because Dr. Olivieri and her clinic medical staff wrote several prescriptions for it in the first half of February 1997 (see section 5K).

In summary, despite the facts that some patients had run out of the drug and Dr. Koren had again been agreed on as an intermediary in the supply, Apotex did not reinstate it in a timely manner. Factors other than relations between Dr. Olivieri and the company must therefore have been involved in the second stoppage in the supply. Two possibilities emerge from the documentary record available to this inquiry. One is that during the late summer and fall of 1996, there were disagreements between Apotex and Dr. Olivieri, and between Apotex and Dr. Brittenham, over provision of close-out data and earlier data from the terminated trials to Apotex. Following the termination of the trials and Apotex's legal warnings to Dr. Olivieri, Dr. Brittenham refused to supply audited source data on hepatic iron concentrations to the company, except on terms he specified. Apotex refused his terms¹⁴ and it had no relevant contract with him for either the LA-01 or the LA-03 trial it could enforce to get the information on its terms. However, Dr. Olivieri provided an extensive amount of organized post-trial (close-out) data, as well as pre-termination data from both trials on November 15, 1996. Receipt of this data was acknowledged by the company,¹⁵ but it still did not reinstate the supply of L1 until many weeks later, as noted above.

Another possible factor was the one Dr. Olivieri said Ms. Klein reported to her in late October 1996: that Apotex had stopped supplying the drug because it was concerned that she would "report" the results of monitoring the patients. Under EDR she was obligated to monitor them because she was legally obligated to "report" the results of treatment to Health Canada, as well as legally and ethically obligated to report any adverse reactions to patients. We do not have a statement by Apotex from October 1996 that would either corroborate or dispute the report of Ms. Klein to Dr. Olivieri. However, we do have the modified LA-03 protocol that Apotex had proposed in April 1995 that would have eliminated one monitoring procedure, annual liver biopsy, which was used for determination of hepatic iron concentration (HIC) and for histology (see section 5D). We also have a written statement by Apotex dated March 7, 1997 that it had objections to the use of liver biopsy. In addition, on the day before, March 6, 1997, Apotex proposed to administrators in both HSC and The Toronto Hospital that use of L1 be expanded, but using a monitoring regime that did not include annual liver biopsy. (This 1997 Apotex correspondence is cited and discussed in section 5Q.)

Summary and Conclusions

1 | Following the terminations by Apotex in late May 1996, both the LA-01 and LA-03 trials were closed out, and close-out assessments and data compilation were completed by the end of October 1996.

2 | Those patients who continued under EDR were monitored by Dr. Olivieri using the same diagnostic tests as had been used during the trials, to ensure the safety of patients and to comply with reporting requirements.

3 | Apotex again showed disregard for the interests of patients and the concerns of patients and their parents when it stopped the supply of L1 in the fall of 1996, as it had in May 1996. This action by Apotex cannot be justified or adequately explained either by disagreements between Apotex and Dr. Brittenham or Dr. Olivieri over the provision of data, or by the working relationship between Olivieri and Apotex.

4 | There was a report by Ms. Klein that the fact that Dr. Olivieri was monitoring patients, and would thus be able to “report” results of treatment (as legally and ethically required), was a factor in Apotex’s action to stop the supply. This was not directly corroborated by other reports, but there is also no documentary information from the time to the effect that this was not a factor.

5 | There is no record that any of Drs. Koren, Aberman, Goldbloom, or Freedman (who were involved in the November 13, 1997 meeting with Apotex) considered involving the REB over the matter of Apotex’s second stoppage in the supply of the drug. This was an event that they apparently considered adverse to the interests of patients, because they intervened in an effort to have the supply reinstated. Therefore it is reasonable to conclude that these administrators correctly understood that the patients were not in a research trial. Indeed Dr. Goldbloom’s notes on the meeting refer to again reinstating the supply of L1 under the “Emergency Drug Release”¹⁶ program, as had been arranged in June 1996 after Apotex stopped the supply the first time.

6 | Dr. Olivieri’s letter of October 28, 1996 to Dr. Koren, copied to Dean Aberman and Ms. Klein, again put on record that both trials had been “terminated” by Apotex, and that patients who had been participants in the trials were no longer “enrolled” in trials, but instead were receiving the drug under EDR.

5K | Identification of the second risk

(1) Concern arising from an animal model

IN EARLY DECEMBER 1996, Dr. Olivieri went to a meeting of the American Society of Hematology (ASH) in Orlando. After arrival she was contacted by Dr. Brittenham who had just read an article on an animal model study of an iron-chelator chemically similar to L1. The article reported that the chelator had caused progression of liver fibrosis in iron-loaded animals.¹ Dr. Olivieri and Dr. Brittenham then became concerned that L1 might possibly pose this risk to patients. She called her staff in Toronto and arranged for serial liver biopsy slides of several patients in the long-term trial (those that could be located quickly) to be faxed to her. She and Dr. Brittenham reviewed the slides and observed that there was progression of fibrosis in a subset of these patients.

In her scheduled talk in the meeting, Dr. Olivieri reviewed current developments in L1 studies. She reported results from the trials in Toronto, including the finding of loss of sustained efficacy. She noted that both of these trials (LA-01 and LA-03):

were terminated prematurely by their corporate sponsor, the generic drug company Apotex, in May of this year.²

Dr. Olivieri noted that in the same meeting Dr. Victor Hoffbrand was presenting a similar finding of loss of sustained efficacy from his study in England.³ She next summarized the findings of the reported animal model study and said:

To determine whether these remarks have clinical relevance, we have *begun* to examine the progression of liver histology in patients in our long-term treatment cohort.⁴ (emphasis added)

Dr. Olivieri then displayed the faxed biopsy slides which indicated progression of fibrosis in some cases but not in others. She closed her talk with a suggestion that this new question would be pursued. Dr. Spino of Apotex was in the audience and during the question period he criticized Dr. Olivieri's work on L1, saying she was wrong on matters pertaining to L1 and nobody agreed with her, including her own co-investigator in Toronto (a reference to Dr. Koren).⁵

(2) Identification of a risk to patients

Dr. Olivieri's remarks at the ASH meeting were used subsequently by Drs. Koren and O'Brodovich as a basis on which to allege she knew at that time that L1 could cause fibrosis.⁶ They said that she was therefore at serious fault because she did not tell her patients and others until February 1997. However, we have seen no evidence to indicate she knew of, or stated, that there was a causal connection "between the administration of deferiprone and the development of hepatic fibrosis"⁷ at that time. The situation required an expert liver pathologist to assess the slides and sophisticated analytical techniques to determine whether L1 itself could be a cause, before conclusions could be reached as to whether there was a risk or not. Progression of liver fibrosis is not a problem of acute toxicity; it develops slowly. Biopsy slides extending back over several years had to be reviewed, along with other components of patients' medical records. The observed progression of fibrosis in a few patients could have been due to other causes, such as iron loading, or hepatitis C viral infection, or both in combination. It would have been irresponsible for Dr. Olivieri to have come to conclusions before doing a proper analysis. However, it was important to make known that this was a question requiring study.

Upon return to Toronto, Dr. Olivieri spent considerable time gathering annual liver biopsy slides from clinic records and medical archives of both the Hospital for Sick Children and The Toronto Hospital (where adult thalassemia patients received their care).⁸ These were on nineteen patients who had been in the former LA-03 cohort for more than one year, so that Dr. Olivieri was able to assemble sufficiently many serial biopsy slides to enable a determination of the issue.* Dr. Ross Cameron, a liver pathologist in The Toronto Hospital and professor of pathology in the University who had worked with Dr. Olivieri on biopsy data from the L1 trials since 1990, agreed to review them on very short notice.⁹ He began during the Christmas–New Year period and completed an initial review by mid-January, reaching the preliminary conclusion that L1 was the probable cause of progression of fibrosis observed in some of the patients in the group of nineteen.¹⁰ The analysis showed that other possible factors were not significant.

Together with Drs. Brittenham and Cameron, Dr. Olivieri started to make arrangements to inform patients, Apotex, the regulators and the scientific community. Dr. Olivieri was required by ethical norms and law to inform patients, and by law to inform Apotex and the regulators. It was also

*Liver biopsy slides from patients in this group extended back to 1990. The long-term study (LA-03) had had a larger number of patients enrolled for varying periods of time; each of these nineteen had been enrolled for sufficient time for slides from at least two serial biopsy analysis to be available for review.

important to inform the scientific community, because L1 was being administered in research trials in several countries, and in India it was licenced for therapeutic use. Dr. Olivieri reported to us that she felt it virtually certain that Apotex would exert even stronger pressure to prevent the information on this new risk of L1 being released, because it was more likely to affect Apotex's licencing prospects adversely than the risk of loss of sustained efficacy.

Drs. Olivieri and Brittenham completed a draft report to the regulators on January 22, 1997. They gave it to Dr. Cameron for his review and approval. At that point Dr. Cameron felt he should re-check his analysis, because it would be wrong to unnecessarily alarm patients and it also would expose Dr. Olivieri to legal retaliation by Apotex if he had made a serious error. This took approximately two weeks, and was not completed until "early February."¹¹ Dr. Cameron's first analysis was confirmed and he then agreed to co-sign a report to the regulators. It was only then that Dr. Olivieri could say that L1 did pose a risk of progression of fibrosis.^{12*}

The report was addressed to the regulatory authorities and recommended that L1 not be licenced for therapeutic use. This was on the basis of the two risks, loss of sustained efficacy and progression of liver fibrosis, the latter described in the report as a "severe adverse reaction." The report referred to earlier studies on iron metabolism and suggested that the exacerbation of fibrosis by L1 occurred in the presence of iron loading (as in the animal study on a related chelator¹³). The report concluded:

Because our long-term prospective study of deferiprone has been observational rather than a randomized, blinded clinical trial, and because the adverse effect on hepatic fibrosis has not been confirmed by challenge and de-challenge, the relationship cannot be classified as *definite*. Nonetheless, in the absence of other established causes for the progression of hepatic fibrosis and in view of the lack of an increase in mean hepatic iron, the relationship must be considered *probable*, and on clinical grounds, highly likely.¹⁴ (emphasis in original)

The authors also said that the finding was disappointing to them: "Given the hope, time, effort and resources that have been invested in this compound, we deeply regret this outcome."¹⁵ Dr. Olivieri and Dr. Brittenham had devoted much of the preceding several years to the development of this drug, in the hope that it could be a safe and effective treatment for patients with a very serious

*Dr. Cameron, Dr. Brittenham and Dr. Olivieri neglected to change the date on the report to regulators from January 22, 1997, the date of the draft prepared on the basis of Dr. Cameron's preliminary findings. The fact that it bore this date, rather than a date in early February when identification of the risk was confirmed, was a contributing factor to subsequent misunderstandings and controversy.

disease, for which the only proven therapy was the onerous deferoxamine regime. Their 1995 publication had encouraged widespread hopes for the drug (see section 5C(1)).

The report to the regulators set out recommended alternatives for patients, principally return to standard therapy—subcutaneous infusion of deferoxamine—even if at suboptimal dosages which patients would find easier to comply with.¹⁶ In support of this recommendation the report cited studies showing that, “deferoxamine arrested hepatic fibrosis even when given in suboptimal doses that only stabilized rather than reduced the hepatic iron.”¹⁷

(3) Balancing of risks for patients in the short term

The clinical situation for patients currently on L1 was a more complex matter than a recommendation to regulators against future licencing. Patients in the former LA-03 trial cohort had previously agreed to try L1 because they were unwilling or unable to comply with the standard therapy for reducing iron load. Not being on any iron-chelation drug put them at risk for the certain toxicity of iron loading, as they had to continue to receive blood transfusions for their anemia. Both toxicity from iron loading, and toxicity from L1 were long-term, not acute effects.* The situation for patients in the short term was therefore one of balancing risks between two chronic toxicities. On the one hand, an experimental treatment for iron toxicity, L1, was now found to be a probable cause in some patients of an adverse effect it was intended to prevent, namely, progression of liver fibrosis. On the other hand, not being on any chelation treatment for an extended period exposed patients to the known risks of iron loading, including progression of liver fibrosis and cardiac disease. Chelation treatment could, however, be interrupted safely for a short period, the duration depending on the individual patient’s tissue iron burden. Because of the onerous nature of the standard therapy, it would have to be explained to patients how and why it was in their best interests to return to it.

(4) Fulfilling reporting obligations

Having identified a risk, Dr. Olivieri was obligated to inform patients, under national and international norms of clinical ethics for physicians. As “the practitioner” for the administration of L1 under the EDR provisions of the *Food and Drugs Act and Regulations*, she also was legally obligated to inform “the manufacturer” (Apotex) and the federal regulators. She had no additional

*In an article on this risk of L1 published in the *New England Journal of Medicine* in August 1998, Dr. Olivieri and her co-authors reported that, “the median time to progression of fibrosis was 3.2 years” for patients in the LA-03 group.

reporting obligations because the patients were not (since May 1996) in any research trial.

Because she continued under unrescinded legal warnings from Apotex, Dr. Olivieri had consulted her CMPA counsel Mr. Mason about fulfilling her reporting obligations, in the event Dr. Cameron confirmed that there was a risk. Mr. Mason again advised her to take the staged approach that CMPA had been advising since the summer of 1996: inform Apotex first, then wait for a response from Apotex before proceeding to inform anyone else.¹⁸

Informing patients. As Dr. Cameron was conducting his review of biopsy slides, Dr. Olivieri consulted with Dr. Michael Baker, Physician-in-Chief of The Toronto Hospital (TTH), himself a hematologist.¹⁹ She had recently been appointed as director of the hemoglobinopathy program in the adult hospital. It was in the adult hospital that almost all of the patients remaining in the long-term treatment group were by then receiving their care,²⁰ and it was in data of this group the risk was identified. Because they had been on L1 longer, their risk was also greater than those in the former LA-01 cohort.

Dr. Olivieri reported to us that in late January 1997 she informed all staff in the thalassemia clinics in both hospitals of the review of historical biopsy data being conducted and the reason for it. Pending completion of Dr. Cameron's review, she asked the assisting physicians to discuss the need for early liver biopsies with patients as they came in to the clinic for their regular blood transfusions, if they had not had a biopsy recently. The few patients who came in during this brief period were advised only that an unspecified concern had arisen. However, once Dr. Cameron had completed his review in early February, Dr. Olivieri informed all physicians and other professional staff in both the HSC and TTH clinics that the risk had been scientifically identified and asked them to organize and publicize an information meeting for patients. (See section 5P.)

In this instance, Dr. Olivieri did not follow the staged approach advised by the CMPA. Instead she began informing patients of the new risk on February 4, the same day she advised Apotex. Dr. Olivieri's first group information meeting, for adult patients from both treatment groups (patients from the former LA-01 and LA-03 cohorts), was held in the early evening of February 4.²¹ Dr. Cameron attended to explain his findings, and Dr. Melanie Kirby (Dr. Olivieri's associate in the TTH clinic) and Ms. Kathy Netten (the social worker for the thalassemia program) also attended.²² Dr. Olivieri reported to us that patients were very distressed about the prospect of possibly having to stop using L1 and return to the onerous standard therapy. Some asked whether the observed progression of fibrosis could have been attributed to hepatitis C viral infection, which many had experienced from

blood transfusions. Dr. Cameron explained that this possibility had been carefully considered and determined not to have been the cause of the observed progression of fibrosis in the data on the LA-03 group.

During the next two weeks, Dr. Olivieri personally contacted all 14 patients (or their families) in HSC who were on L1 to explain the situation. She or Dr. Kirby also personally contacted each TTH patient who had been unable to attend the February 4 meeting. Dr. Olivieri counselled patients to interrupt use of L1 pending the results of their liver biopsy, which she also counselled they have if they had not recently had one.²³ The purposes of the liver biopsy were to determine:

- the future course of therapy for each patient;²⁴ and
- whether a patient had experienced progression of fibrosis while on L1.²⁵

Dr. Olivieri's individual counselling of HSC patients and families to interrupt use of L1 had the result that, by February 20 or earlier, all HSC patients had "agreed to temporarily interrupt deferiprone therapy until a liver biopsy is obtained in each child."²⁶ During the first two and a half weeks of February, prescriptions for L1 were written for several patients, because of the concern to balance risks and benefits in individual cases (a patient with a very high HIC level was at greater risk from the chronic toxicity of iron loading, in the absence of any chelation). However, February 18 was the last date on which prescriptions for the drug were filled by the HSC pharmacy.²⁷ Some adult patients treated in TTH initially did not wish to stop, and one or two continued until May.* Dr. Olivieri arranged for a second group meeting of patients and families on March 6 to provide them with current information and to discuss the situation further.²⁸ In this meeting, she outlined to patients the reasons why she and Dr. Brittenham believed that L1 should no longer be used for the treatment of iron overload. She also explained treatment alternatives, which would depend on their biopsy results.

Informing Apotex. On February 4, 1997 Dr. Olivieri forwarded to Apotex through her CMPA legal counsel Mr. Colangelo a copy of her report addressed to the regulators. Her counsel advised Apotex that she intended to send this report directly to the regulators on February 10, but was providing it to Apotex in advance. He added:

*At various times in the period from February to May 1997, as well as later, Apotex staff were endeavouring to persuade medical administrators in both hospitals and adult patients that L1 was effective and safe. (See subsection 5K(9).)

If it is the intention of Apotex to commence legal proceedings to attempt to restrain Dr. Olivieri ..., then I am instructed to accept service on her behalf ...²⁹

The initial response from the company was to ask that Dr. Olivieri delay sending her report to the regulators.³⁰ This was followed by a strongly worded lawyer's letter of February 11 (quoted in section 5I(1)) telling her not to communicate the new risk to anyone, at least until after an Apotex consultant reviewed the data.³¹

Informing the regulators. On CMPA legal advice, Dr. Olivieri delayed sending the report to the regulators for two more weeks. On February 24, she forwarded the report (co-signed by Drs. Brittenham and Cameron) to the FDA, HPB, and the Italian and Indian health ministries, despite Apotex's requests for further delay and despite the company's ongoing warnings to her of legal consequences. (Developments involving regulatory agencies are discussed in section 5U.)

Conclusion

Dr. Olivieri fulfilled all of her reporting obligations, both ethical and legal, in a timely manner.

(5) Informing other scientists

On the basis of Dr. Cameron’s preliminary findings, on January 16, 1997 Drs. Olivieri and Brittenham had sent out abstracts for conferences to be held in March and April, on the basis that they would withdraw the abstracts if, on re-checking his analysis of the biopsy slides, Dr. Cameron found he had erred. They judged that physicians administering L1 in other centres should be alerted to the new risk. Conferences have deadlines for abstracts, although minor delays in submissions may be allowed.*

On February 5, the day after Dr. Olivieri informed patients and Apotex, she provided a copy of her report on the risk to Dr. Koren through one of their joint CMPA legal counsel, Mr. Colangelo.³² According to the wording of the Apotex legal warnings to Dr. Olivieri, she was not to communicate with “third parties” in relation to the LA-01 contract, but there was no restriction on informing Dr. Koren, as he was a party to that contract. Thus, Dr. Olivieri was not under legal warning against informing him, and she informed him very promptly following Dr. Cameron’s confirmation that there was a risk. Under the EDR regulations, she was not obligated to inform him. By his own written accounts, he was no longer involved with the patients after the trials were terminated in May 1996,³³ but sometimes acted as an intermediary for the supply of L1, so it was appropriate to inform him of the new risk (see sections 5G(1) and 5J(3)).

Drs. Olivieri and Brittenham also had discussions with their American co-investigators on a proposed study involving use of L1 to treat patients with sickle cell disease (SCD). It was decided that the start of this trial should be delayed until the new risk of L1 was better understood. The proposed funding agency (National Institutes of Health) was so advised.³⁴

Conclusion

Dr. Olivieri initiated steps to ensure that the international scientific community would be advised in a timely manner, by sending abstracts to organizers of several conferences scheduled for the late winter and early spring of 1997. Dr. Koren was promptly advised. The co-investigators for the proposed SCD study were also promptly advised.

(6) Interventions by Dr. O’Brodivich & Dr. Moore

*Dr. O’Brodivich later alleged to the Naimark Review (in his memo dated September 24, 1998) that one of these abstracts must have been sent out on or before the deadline for the conference, January 10. However, the fax transmission date of January 16 is documented and the abstract was accepted, although submitted late. (Developments concerning these abstracts are discussed section 5I(1).)

The controversy took on wider dimensions after Dr. Spino contacted Dr. O’Brodivich on February 18, 1997, the day the HSC pharmacy last dispensed L1.

In the evening of February 18, 1997, Dr. Spino contacted Dr. O’Brodivich to ask if he was aware of Dr. Olivieri’s opinion that she had observed “*a severe adverse reaction*” to the use of L1.³⁵ (emphasis in original)

No additional information on the contents of this conversation is available. However, we know that Apotex legal counsel had written to Dr. Olivieri a week earlier, stating that her finding of a new risk was “not... scientifically valid,” that it would be injurious to Apotex’s “business,” and that she should not inform “patients and their doctors.”³⁶ It is ironic that Apotex contacted the Pediatrician-in-Chief, after having expressly warned Dr. Olivieri not to advise patients or their physicians, since Dr. O’Brodivich subsequently criticized Dr. Olivieri for allegedly not informing these physicians.

Dr. O’Brodivich then obtained a copy of Dr. Olivieri’s report from Dr. Koren. Dr. Koren was later to allege that Dr. Olivieri was at fault for not informing the REB, Dr. O’Brodivich and himself about the new risk. However, Dr. Koren was sent the full report on February 5 and (by his own later account) received it shortly thereafter,³⁷ yet he told no one until contacted two weeks later by Dr. O’Brodivich and asked about it. Indeed he alleged to the Naimark Review that he knew of the risk of liver fibrosis in mid-December 1996. He did not explain, if this was so, why he did not tell anyone of the new risk until Dr. O’Brodivich contacted him on February 19. (See sections 5O, 5P and 5R.)

Dr. O’Brodivich now conducted himself as if this was a matter requiring his immediate intervention and called:

An Emergency meeting (re: patient safety related to continued use of L1 at Hospital for Sick Children).³⁸

This was held at 3:00 PM on February 19. Dr. Olivieri reported to us that Dr. O’Brodivich severely criticized her for not informing persons he alleged should have been informed, including himself.³⁹ In fact there was no administrative requirement to inform him, and no medical purpose, because he is not an expert in thalassemia. The minutes record that Dr. O’Brodivich:

questioned whether the REB ha[d] been notified and wanted to discuss the potential risks being faced by patients in all HSC based research studies involving L1 in Humans and review actions taken to minimize the risk to those patients referred to in the most recent findings.⁴⁰

Dr. O’Brodivich also requested a written account from Dr. Olivieri “within the next day or so, [on] the appropriate clinical action which should be taken.” On the same day, he also “notified the REB of Dr. Olivieri’s conclusions.”⁴¹ Dr. Moore, the REB Chair, thereupon conducted herself as if

the REB had jurisdiction. The next day, February 20, she wrote to Dr. Olivieri:

According to hospital and MRC policy such adverse events should be reported to the REB so that the suitability of continuing patients on the agent can be *determined*.... I would be grateful if you could inform me as soon as possible what course you are recommending for the patients currently enrolled in the study.⁴² (emphasis added)

However, as discussed earlier, the trials and protocols had been terminated in May 1996. The REB was informed in writing of the terminations, and of the fact that the patients had “been withdrawn” from the research trials.⁴³ The *Terms of Reference* of the REB provide for:

- prior review of research protocols to assess them for “scientific and ethical standards;” and
- safeguarding the interests of “patients and members of the community who serve as research subjects.”⁴⁴

In this case the patients in question had ceased being research subjects in May 1996 and there was no longer any active protocol, so the REB had no jurisdiction over them and no protocol to administer. Consequently, contrary to Dr. Moore’s assertion, there was in fact no requirement in Hospital or MRC policy that Dr. Olivieri report to the REB. Dr. Moore had mistaken the fact that patients were continuing on the drug under EDR, with their continuing in a research study (see section 5H(1)).

Nevertheless, Dr. Olivieri promptly replied to the requests of both Drs. O’Brodivich and Moore. On February 20, she sent letters to both of them, explaining the measures she had already undertaken to manage patient care, and outlining other measures in progress, as well as the clinical basis. In particular, she advised both Dr. O’Brodivich and Dr. Moore that these measures included scheduling early liver biopsies for patients who had not recently had one, and she outlined the clinical reasons.⁴⁵ Dr. O’Brodivich did not object, or use his administrative authority to prevent these liver biopsies (see section 5Q). Dr. Moore’s response to the scheduling of the biopsies was one of approval (though in fact she had no authority to approve or disapprove), coupled with a request, “Please keep me informed regarding your findings [from the results of the biopsies].”⁴⁶

The degree of Dr. O’Brodivich’s objection to what he considered to be Dr. Olivieri’s failure to report the new risk to the REB, and to himself, was such that he considered formal action against her. The entry for February 24, 1997 in the chronology he provided to the Naimark Review said:

... discussions with [HSC legal counsel] Bill Carter regarding a disciplinary action and also necessity of reporting to the College of Physicians and Surgeons.⁴⁷

Dr. O’Brodivich apparently did not know, and did not inquire whether the REB *had* jurisdiction until a week *after* he notified Dr. Moore and she became involved. On February 26, he wrote to Dr. Moore and asked two questions:

1. What is the present status of REB approved research studies involving L1? Are any continuing? If they have been discontinued, I would appreciate confirmation as to the date of termination. In both cases, I would appreciate a copy of the REB approved protocol for L1 studies.
2. Does the REB have any role or obligation regarding emergency release [EDR] of L1 *subsequent to termination* of a previously REB approved study?⁴⁸ (emphasis added)

(7) Errors by Dr. Moore

Dr. Moore replied to Dr. O’Brodivich’s questions the next day, February 27. In her reply, she provided incorrect information—information that was contradicted by the documentary record available to her as REB Chair. However, her incorrect information was used a basis for actions against Dr. Olivieri by Dr. O’Brodivich, both then and later. Her incorrect information was also relied on by the Naimark Review and the Medical Advisory Committee (MAC) in reaching their incorrect conclusions on these issues (see sections 5O and 5P).

Dr. Moore’s answer to the Dr. O’Brodivich’s first question was that, “the randomised study of L1 (REB # 91/620) [LA-01] was terminated on May 24, 1996,” but that “some patients ... were continued on the other study ... (REB # 90/523) [the long-term trial, LA-03]” and it had been “renewed in September 1996.”⁴⁹ She was correct regarding LA-01, but incorrect regarding LA-03. It is clear from her own written record that Dr. Moore had been misinterpreting the documents available to her as REB Chair since July 1996 (see section 5H(1)).⁵⁰ Apotex had the right under the contracts for both trials (and also under the protocols) to terminate them at any time, for any reason, and that is what the company did. That is also what the REB files show, in the formal notifications provided by Drs. Olivieri and Freedman, stamped as received by the REB on August 1, 1996.⁵¹ A review of these files by Dr. Moore would have shown this. Her erroneous views are contained in REB records and in her own correspondence throughout her three-year term as Chair.

Dr. Moore repeated the errors contained in her February 27 letter to Dr. O’Brodivich in another letter to him on June 3, 1998, and again in her testimony to the MAC on January 11, 1999. In view of the importance of subsequent events that were influenced by these errors, we review them here. In her letter of June 3, 1998, Dr. Moore wrote:

If funding ceases from one source it does not negate or terminate REB approval.... Concerning Dr. Olivieri’s deferiprone research, these studies commenced in 1989/90, and have had a number of sponsors, including MRC, NIH and Apotex from 1994. When Apotex withdrew its sponsorship in May 1996, some patients (following detailed information sessions by Dr. Olivieri) continued in the compassionate use trial [LA-03], but this was not regarded as a new trial and its REB approval was maintained. The only change was modification of the consent forms detailing lack of efficacy in a subgroup of patients. Thus this study continued with full REB approval.⁵² *

The summary of Dr. Moore’s testimony to the MAC recorded:

Dr. Moore explained that there is a distinction between termination of funding for research and the termination of a study. In the case of deferiprone, the original study was funded by the MRC and was later funded by Apotex. When Apotex withdrew, it reverted to an MRC study.⁵³

Dr. Moore’s belief that the long-term trial had been “renewed in September 1996” was mistaken. The REB had neither the legal nor the administrative authority to “renew” a terminated trial of the drug L1. The manufacturer and owner of the drug, Apotex, had the legal right to terminate both trials. Apotex exercised this right in May 1996, informed Health Canada that it had done so, and refused to reinstate any trial. Apotex also could, and did, stop the supply of its drug at will. The REB was formally notified of the terminations by the principal investigator, Dr. Olivieri, in July 1996. After the terminations in May 1996, there was no sponsor, no investigator and no active protocol for any L1 clinical trial in Toronto. There was only the non-trial EDR treatment arrangement. (See sections 5F, 5G, 5H, 5J and 5K(9).)

It appears (although her wording, quoted above, was imprecise) Dr. Moore also incorrectly supposed that those patients who had been enrolled in the L1 treatment arm of the randomized trial LA-01 (that she herself stated “was terminated”), and who had continued on L1 under EDR, had somehow then been enrolled in the long-term trial LA-03 which was, she thought, continuing. However, the (terminated) protocol for the randomized trial LA-01, in which these patients had formerly been enrolled, was substantially different from the (also terminated) protocol for the long-term trial LA-03 into which Dr. Moore erroneously supposed they had been newly enrolled in the summer of 1996. No new protocol, or modified protocol for a renewal of LA-03, to enrol a different group of patients had been submitted or approved, a fact Dr. Moore

*Dr. Moore copied Dr. Olivieri on her June 3, 1998 letter to Dr. O’Brodivich. Dr. Olivieri then wrote to Dr. O’Brodivich on June 8, 1998 providing the correct information—that on “24 May 1996... Apotex Inc. terminated these [LA-01 and LA-03] trials.” It appears that Dr. O’Brodivich recognized this fact, because in a letter to Dr. Spino on June 10, 1998 he noted “Apotex’s cancellation of the clinical trials [of L1] in May 1996,” and copied Dr. Olivieri on this letter.

herself appears to have acknowledged in her letter of June 3, 1998 to Dr. O’Brodivich.⁵⁴ As noted above, the fact is that no trial of L1 continued—those patients from each of the two former trial cohorts who continued on the drug were treated under a non-trial EDR arrangement.

Contrary to another statement by Dr. Moore, the long-term trial (REB # 90/523, also termed LA-03) could not have reverted to “an MRC study.” In 1992, MRC declined to sponsor this trial beyond 1993, and had awarded a “terminal” one-year grant for 1992-1993. It was in fact the randomized trial LA-01 that MRC had co-sponsored with Apotex for 1993-1996, and this was the trial that Dr. Moore herself stated “was terminated.” The 1993 application to MRC for funding for the randomized trial was very specific as to cohort size, rationale, methodology and budget and could not reasonably be confused or conflated with the LA-03 trial, even if they had not both been terminated in May 1996 by Apotex. (See sections 5A(1) and 5A(2).)

Other errors in Dr. Moore’s letters to Dr. O’Brodivich further suggest she either did not carefully review, or did not understand, the documentary record available to her as REB Chair. She wrote that Apotex funding was “from 1994.” In fact, as set out in the payment schedules in the two contracts, Apotex funding for LA-01 began in 1993, and for LA-03 in 1995, not 1994 in either case. Dr. Moore also wrote that the Toronto L1 trials had “NIH” funding, but here again it appears she either did not carefully review, or understand, the record. Some patients had liver iron determinations by SQUID in Dr. Brittenham’s laboratory in Cleveland, and his laboratory received NIH funding for other studies he carried out, but he was never an “investigator” in the Toronto trials. It was Apotex funding that paid transportation expenses for patients to travel to Cleveland. Dr. Moore referred to “Dr. Olivieri’s deferiprone research,” so possibly she confused the two trials of L1 in thalassemia, that Apotex had terminated, with a proposed multi-centre trial of L1 in sickle cell disease (SCD), for which NIH was the intended source of funds. However, the SCD study was only a proposal and it had nothing to do with the use of L1 in thalassemia (see section 5K(8)).

In her February 27 reply to Dr. O’Brodivich’s second question, as to whether the REB had any role or obligation regarding emergency release [EDR] of L1 subsequent to termination of a previously REB approved study, Dr. Moore did not respond to the question actually posed to her. She answered in general terms that might apply to some but not all cases:

In answer to your second question as to the role or obligation of the REB regarding emergency release of a drug to previous study participants, if it is thought that emergency drug release is in the patient’s best interests, the

Board [REB] has felt it has an obligation to recommend release and the supplier has been informed.

Her answer did not apply in this case and the facts demonstrating that it did not were available to Dr. Moore in documents. The point is that the REB could approve emergency drug release (EDR), if asked, but REB approval was not required for EDR at HSC, and in this case, the REB was not asked. This EDR arrangement had been mediated on June 7 by Dean Aberman directly between Apotex and Dr. Olivieri—the REB was not involved, because there was no requirement for it to be. Dr. Moore’s reply to the second question again suggests she had not carefully examined, or did not understand, the documents. However, her answer apparently was taken by some as implying that the REB had approved this EDR arrangement whereas, in fact, it had not. Thus her answer had the effect of being misleading.

Dr. Moore’s misunderstanding of the situation actually could have been corrected in a meeting on February 27 attended by herself, her predecessor as REB Chair Dr. Zlotkin, Dr. Olivieri and CMPA counsel Mr. Colangelo. Detailed notes were taken by Mr. Colangelo and he recorded that:

Dr. Olivieri took Drs. Zlotkin and Moore through a careful history of the events.... Dr. Zlotkin indicated that if the study is over, then if Dr. Olivieri was continuing to follow these patients as a clinician, then all that would be required would be the proper disclosure of the risks and benefits of treatment. Indeed, it appeared that that had already been done.

...

In these circumstances, Drs. Zlotkin and Moore were quite satisfied that Dr. Olivieri had acted quite appropriately in the circumstances. ... Dr. Olivieri feels that [although not obligated] she would be keeping the Research Ethics Board advised from time to time so that they would be aware of what was happening [but not because there was any obligation for her to do so].⁵⁵

This meeting occurred on the same day that Dr. Moore replied in writing to Dr. O’Brodivich’s questions, providing the incorrect and misleading information discussed above. We do not know which occurred first, the writing of her letter, or her meeting with Drs. Zlotkin and Olivieri. In either case, she failed to correct the record. Had Dr. Moore corrected her misinformation, she would have told Dr. O’Brodivich he had no basis to suppose anything inappropriate had occurred, so his strong criticism of Dr. Olivieri on February 19 had no foundation.

After February 19, because of Dr. O’Brodivich’s insistence, Dr. Olivieri kept Dr. Moore apprised of developments. In her responses, Dr. Moore indicated approval for all of Dr. Olivieri’s actions in managing patients (although she had no mandate to approve or disapprove). She appears to have continued to believe that she was acting under the REB mandate in regard to treatment of patients with L1, throughout her three-year term of office. In fact,

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the REB mandate did not apply to this EDR arrangement at any time during her term of office.

Conclusions for Subsections (6) and (7)

1 | Dr. O’Brodivich, who is not an expert in thalassemia, incorrectly assessed the situation as requiring his emergency intervention when, in fact, the situation was one of balancing risks between two chronic toxicities and Dr. Olivieri had the clinical management of patients well in hand.

2 | Dr. O’Brodivich had no basis for his criticism that Dr. Olivieri had not informed the REB or himself of the risk of progression of liver fibrosis.

3 | Dr. O’Brodivich did not object to, or try to prevent the liver biopsies Dr. Olivieri scheduled for patients who had been on L1.

4 | Dr. Koren was fully apprised of the new risk by Dr. Olivieri “in early February 1997.”⁵⁶ He did not inform the REB. He also did not inform Dr. O’Brodivich until after Dr. O’Brodivich learned of the identification of the new risk from Apotex and asked Dr. Koren about it on February 19. We have seen no explanation for the fact that Dr. O’Brodivich did not subject Dr. Koren to the same criticism as Dr. Olivieri.

5 | Dr. Moore provided incorrect and misleading information to Dr. O’Brodivich. She said that a research trial of L1 continued after May 1996 and that the REB had jurisdiction over patients who continued on L1 under the EDR arrangement mediated by Dean Aberman. This was not the case.

6 | Dr. Moore was provided with the correct information on the termination of the trials by Dr. Olivieri on February 27, 1997 (as she had earlier, in July 1996, in writing, in documents that REB had actually received). However, Dr. Moore never subsequently corrected her written record and continued making erroneous statements on these matters in 1998 and 1999.

7 | Dr. Olivieri was not required to report to the REB. When she did report, on the insistence of Dr. O’Brodivich, it made no material difference to the care of patients.

(8) Further actions by Dr. O’Brodivich

When Dr. O’Brodivich intervened administratively on February 19, 1997 and caused the REB to be involved, Dr. Moore supposed that the REB would determine the suitability of continuing patients on L1. The next day, February 20, Dr. O’Brodivich wrote to inform Dr. Baker at The Toronto Hospital of his action:

I have... taken the following action. I have notified the Research Institute of the Hospital for Sick Children and the Chair of the Research Ethics Board (Dr. Aideen Moore) and indicated my concern. I have recommended to the Chair of the Research Ethics Board that the REB re-evaluate all experimental protocols utilizing L1 at the Hospital for Sick Children as to whether or not a detailed external scientific review is required prior to approval of any continued use experimental use of L1.⁵⁷

This letter was copied to Dr. Moore and would have bolstered her (mistaken) impression that the REB had jurisdiction. However, Dr. O’Brodivich himself intervened medically, directing that use of L1 henceforth be “stopped” in HSC.^{58*} In doing so, he in effect assumed the role Dr. Moore supposed the REB had. Dr. O’Brodivich is not an expert in thalassemia, is not known to have obtained any report from independent experts, and had no treatment plan of his own as to what to do next.⁵⁹ He wrote letters to Dr. Olivieri demanding more information on the management of patient care.⁶⁰ She replied that she had already provided to him all available information, and repeated that the future course of therapy for patients would depend on the biopsy results, which were not yet available.⁶¹ In contrast, Dr. Moore appears to have understood the medical point stated both to her and Dr. O’Brodivich by Dr. Olivieri—that future therapy for each patient depended on their biopsy results. She only asked to be informed when Dr. Olivieri was able to prescribe appropriate courses of treatment for the patients.⁶²

As mentioned earlier, on February 24 Dr. O’Brodivich had consulted HSC legal counsel about the prospects of taking disciplinary action against Dr. Olivieri.⁶³ He met with HSC counsel again on March 6, subsequent to receiving correspondence from Dr. Olivieri and her CMPA counsel.⁶⁴ HSC counsel, after reviewing Dr. Olivieri’s account of developments and her actions in management of patient care, advised Dr. O’Brodivich that there

*This action by Dr. O’Brodivich on or about February 28 was redundant, in the short run at least, because by February 20, 1997 Dr. Olivieri had already successfully counselled all HSC patients to interrupt use of L1, pending biopsy results. During the trials and also under the subsequent EDR arrangement, each patient was given a multi-week supply of L1 in a container with a metering device to record compliance. Some of them therefore had supplies lasting weeks beyond the date of Dr. O’Brodivich’s directive. They could also extend the duration of a supply by reducing their ingestion rate. Therefore, Dr. Olivieri’s approach of counselling patients to interrupt was not only successful, but also more appropriate in the circumstances.

were no grounds for disciplinary action against her.⁶⁵ The correspondence from Dr. O’Brodivich to Dr. Olivieri on the risk of progression of liver fibrosis then appeared to end, and the dispute between them over alleged reporting obligations appeared resolved.

However, Dr. O’Brodivich revived the issue of reporting to the REB in the autumn of 1998, during the Naimark Review. In a lengthy memo to Dr. Naimark on September 24, 1998,⁶⁶ he made allegations against Dr. Olivieri, including that she had “failed” in a duty to report immediately her finding of the risk of progression of liver fibrosis to the REB, and suggested that patient safety might thereby have been compromised. (See section 5.O.)

In February 1997 and during the Naimark Review, Dr. O’Brodivich also raised the matter of a draft protocol Dr. Olivieri had submitted for a proposed study of L1 for the treatment of sickle cell disease (SCD). Preliminary studies by American investigators had suggested that L1 might be effective in removing excess iron from membranes of red cells of SCD patients. The proposal was for a short-term (six-month), multi-centre study and an application was to be made to the USA National Institutes of Health for funding. Dr. Olivieri had submitted the proposal for ethical review the previous summer and it was under consideration by the REB. In February 1997, this proposed study had neither REB approval nor funding, and no patient enrolment was anticipated for many months.⁶⁷ Dr. O’Brodivich alleged that Dr. Olivieri was at fault for not immediately informing the REB and himself about the risk of progression of liver fibrosis, in regard to this proposed SCD study. There was in fact no study, and no SCD patients were on L1, so patient safety was not at risk.

It is the case that Dr. Olivieri did not inform the REB of the risk of progression of fibrosis, confirmed in early February 1997, until February 20 when she was requested to do so. However, as noted, in regard to the thalassaemia patients who were on L1, she was not required to inform the REB. In regard to the *proposed* SCD study, she was obligated to inform the REB, but there was no immediacy in this case because no patients would be involved for some considerable time. REB minutes of February 14, 1997 record that this proposal was still under discussion and would not be approved until after further information was obtained from Dr. Olivieri.⁶⁸ Dr. Olivieri provided the full report on the new risk of L1 on February 20. Dr. Moore in reply asked only that she also provide revised patient consent forms for the proposed SCD study, as Dr. Olivieri had already indicated she would.⁶⁹ Dr. Olivieri breached no policy and failed in no obligation in this matter, either.

Conclusions

1 | During a period extending through the last week of February and the first week of March 1997, Dr. O’Brodivich conducted himself as though he did not accept Dr. Olivieri’s medical assessment. He is not an expert in the relevant clinical specialty and we have seen no evidence he consulted independent experts in the relevant clinical specialty.

2 | Although Dr. Moore, having been notified by Dr. O’Brodivich, supposed (incorrectly) that the REB had jurisdiction and would determine the future course of therapy, Dr. O’Brodivich himself intervened medically and by his own account, “stopped the use of L1 at Hospital for Sick Children.”⁷⁰

3 | In regard to the proposed study involving use of L1 in SCD, Dr. Olivieri advised the REB of the risk of progression of liver fibrosis on February 20. In view of the facts that this was not an active study, only a proposal that was not yet approved, and no patients were enrolled, we conclude that Dr. Olivieri did advise the REB in a timely manner.

4 | There was no ethical, clinical or administrative failing by Dr. Olivieri in the matter of the risk of progression of liver fibrosis. Dr. O’Brodivich’s criticisms of her resulted from his misunderstanding the facts.

(9) Return to standard therapy

On March 6, 1997 Dr. Olivieri held a second group meeting for patients and families. She again explained the recently identified risk and the reasons for the liver biopsies that were then in process. She explained why she and Dr. Brittenham had concluded that “L1 should not be used in the treatment of iron overload.”⁷¹ She outlined the process of transferring patients to standard therapy, and explained that the timing of resumption of deferoxamine administration for each patient would depend on the patient’s body iron burden (determined by HIC) and liver fibrosis status.

(10) Promotional efforts by Apotex

On the same day of this meeting, March 6, 1997, Dr. Spino sent a letter to the senior hematologists in both HSC and TTH, Dr. Freedman and Dr. Baker, and proposed that the use of L1 in both hospitals be expanded. Dr. O’Brodivich was sent a copy of this letter by fax. Dr. Spino wrote:

Apotex Inc. has decided to expand its compassionate use program for the drug deferiprone (L1) to patients with iron overload who are unable to take the currently-approved chelation therapy. Now this program will extend to the Hospital for Sick Children (HSC) and The Toronto Hospital (TGH). It has already been successfully implemented in Italy and we believe it is in the

best interest of patients in Toronto to have access to the drug through this program.⁷²

The last sentence is an apparent reference to the short-term safety trial (LA-02 trial), the three main sites of which were Italy, and possibly to an extension of it under a similar protocol called LA-06. Dr. Spino appended to this letter a monitoring schedule that was similar in important respects to protocols LA-02 and LA-06. His appendix referred to a similar draft protocol Apotex had prepared in 1995, termed LA-04. Neither the appendix, nor any of these protocols, included annual liver biopsy for all participating patients for determination of hepatic iron concentration (or SQUID for this) and for histology. Thus it is unlikely that the monitoring regime he proposed now to be followed in Toronto could have led to identification of the two unexpected risks of L1 that was made in data of the LA-03 patient cohort.

Dr. Spino invited Drs. Freedman and Baker to designate physicians willing to prescribe L1 under his proposed patient-monitoring regime, and willing to sign a confidentiality agreement with Apotex. We have no record of any response by Dr. Freedman, or by Dr. O’Brodivich who had just recently “stopped the use of L1” in his hospital. However, Dr. Baker replied to Dr. Spino on April 17, expressing confidence in the staff of the TTH thalassemia clinic (Dr. Olivieri and Dr. Kirby) in their management of patient care. He advised that no TTH physician was willing to prescribe L1 because “its safety has been called into question,” and that no TTH physician was willing to sign a confidentiality agreement with Apotex.⁷³

Dr. Spino concluded his letter to Drs. Freedman and Baker with a statement indicating that (unlike Dr. Moore) Apotex understood that the existing EDR treatment arrangement was not a trial with an active protocol.* He wrote:

We trust that steps can be taken to ensure a smooth transition from the EDR process to one based on a specific protocol for this investigational drug.⁷⁴

By “a specific protocol” Dr. Spino appears to have meant that outlined in his appendix.

In February 1997, Apotex engaged a liver pathologist, Dr. Francesco Callea of Brescia, on a consulting contract to review the same biopsy slides Dr. Cameron had reviewed.⁷⁵ Dr. Callea submitted a preliminary report in April and a final report in May. He found the opposite of Dr. Cameron: “there was a [statistically] significant decline in hepatic fibrosis,” in patients treated with L1.⁷⁶

*As noted in section 5F, Dr. Spino had also recently written to Health Canada (January 25, 1997) and to The Medical Post (published on February 18, 1997) confirming that Apotex had indeed terminated both studies, “LA-01 and LA-03” on May 24, 1996.

In early April 1997 Dr. Tricta of Apotex presented two abstracts at a conference in Malta, co-authored by Dr. Koren and Apotex-funded research fellows. The conclusions in the abstracts were to the effect that L1 was effective and safe and neither mentioned the risk of progression of liver fibrosis. As noted in section 5I, through legal warnings Apotex had attempted and nearly succeeded in deterring Dr. Olivieri from presenting her findings on the two risks at the Malta meeting. She withdrew the abstract she had submitted and only re-submitted it shortly before the conference began, after she obtained (through legal counsel) copies of the the Apotex abstracts.

One of the first persons outside Apotex staff to be informed of Dr. Callea's preliminary report was Dr. O'Brodovich, who attended a meeting on April 18, 1997 where he was informed that, "Dr. Callea's review of the same biopsies presented by Dr. Nancy Olivieri *et al.* revealed no progression of fibrosis."⁷⁷ Dr. Spino wrote to Dr. O'Brodovich a few days after that meeting to summarize the position of Apotex, namely, that Dr. Olivieri's finding of a loss of sustained efficacy "has not been substantiated," and that Dr. Callea's review "revealed no progression of fibrosis."⁷⁸ In support of this position Dr. Spino enclosed copies of several abstracts presented at the Malta conference, including three sponsored by Apotex, and referred to Dr. Callea's preliminary report.

In early May 1997, legal counsel for Apotex refused a request by Counsel for Dr. Olivieri for information on Dr. Callea's review of the biopsy slides, saying that, "Dr. Callea requires some time to finalize his formal report."⁷⁹ In early June, Dr. Spino sent copies of Dr. Callea's report to Drs. Freedman and Goldbloom of HSC, and to Dean Aberman, along with his own detailed synopsis in the covering letter.⁸⁰ The letter said that Drs. Olivieri, Brittenham and Cameron had now also been forwarded a copy of Dr. Callea's report.

On May 8, 1997, Drs. Spino and Tricta of Apotex met with a number of Dr. Olivieri's adult patients. Dr. Olivieri was not invited to this meeting and learned of it by accident. The thalassemia Nurse Coordinator, Ms. Beverley Tyler, and the program Social Worker, Ms. Kathy Netten, attended, but no physicians other than Dr. Tricta were there. Ms. Netten took detailed notes of the presentation by the two Apotex employees. The essence of the information presented by Apotex was that L1 was effective and safe, and that it would be licenced soon in both Italy and Canada. Dr. Callea's report was cited, and reference was made to data from the Apotex-funded trial (LA-02) at Italian sites.⁸¹

In late May 1997, Apotex sent an additional legal warning to Dr. Olivieri, to deter her from presenting her findings at the Cooley's Anemia

Foundation meeting in early June.⁸² Nevertheless, with CMPA legal support, she attended and presented her results. There, Apotex employees criticized her work and presented Dr. Callea's opposing results on liver fibrosis on the issue of whether L1 caused progression of liver fibrosis.⁸³

Following these developments, Dr. Olivieri had the liver biopsy slides reviewed by three independent liver pathologists from England and the USA. All three confirmed Dr. Cameron's finding that L1 was the probable cause of progression of liver fibrosis in some patients. Dr. Olivieri and the liver pathologists published their results in the *New England Journal of Medicine (NEJM)* in August 1998.⁸⁴ It was this publication that initiated widespread coverage of the L1 controversy in the popular press (see sections 5L and 5N).

Conclusion

During the same period when Dr. Olivieri informed patients and parents that L1 should no longer be used and transferred patients from L1 to standard therapy, Apotex took measures to persuade patients and medical administrators in Toronto, as well as the scientific community, that L1 was effective and safe. Apotex did not succeed in persuading Dr. Baker, Physician-in-Chief of The Toronto Hospital. We have no record from this time period of a response to Apotex's proposal by Dr. O'Brodovich, Pediatrician-in-Chief of the Hospital for Sick Children. (However, in his September 24, 1998 submission to the Naimark Review, Dr. O'Brodovich gave more weight to Dr. Callea's consulting report than to the article by Dr. Olivieri and several liver pathologists in *NEJM*.⁸⁵)

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5L | Events at the Hospital, Spring 1997 to Fall 1998

(1) Interventions by Drs. Chan, Dick, Durie & Gallie

DRS. HELEN CHAN, JOHN DICK, PETER DURIE AND BRENDA GALLIE are Senior Scientists in the Hospital's Research Institute and Professors in the University's Faculty of Medicine. Drs. Chan, Durie and Gallie are physicians and clinical researchers; Dr. Dick is a cell biologist. They all have achieved international recognition for their work, and none was a personal friend or scientific collaborator of Dr. Olivieri prior to the L1 dispute.

Dr. Dick was the first to take an interest in the dispute. He was a speaker in the Cooley's Anemia Symposium in early June 1997 at which Dr. Olivieri and Apotex employees presented opposing findings on L1. He told this Committee of Inquiry he was surprised to learn from her that she had received legal warnings from the company not to disclose her findings of risks of L1. She told him that she had the support of her CMPA lawyers to speak at this meeting, but that she expected to have her work criticized by employees of Apotex and other supporters of the company's position.

Dr. Dick attended Dr. Olivieri's presentation and observed the opposition with which her findings were met. Her scientific findings and approach were, however, defended by Dr. David Nathan of Harvard, a leader in the field. Later in the meeting, Dr. Dick spoke with Dr. Nathan who said he was concerned that Dr. Olivieri was being mistreated in Toronto. He suggested to Dr. Dick that he and other colleagues in HSC should intercede. After obtaining more background information from Dr. Olivieri, Dr. Dick had a series of meetings with a number of administrators extending over the next six months. He met most often with Dr. Manuel Buchwald, Director of the Hospital's Research Institute, but also had discussions with Dr. O'Brodovich, Hospital President Mr. Michael Strofolino and Dean Aberman.

In these meetings Dr. Dick tried to interest the administrators in a review of the circumstances of why Dr. Olivieri "felt unsupported" by the Hospital and the University, and why her relations with Dean Aberman and Dr. O'Brodovich "were so broken."¹ Dr. Dick endeavoured to understand the perspectives of the administrators and to act as a mediator between them and Dr. Olivieri. He said he was able to be helpful on minor matters, but encountered what he felt to be defensiveness or rigidity from the administrators on larger matters. By November 1997 he felt that no substantial progress had been made, and expressed his "concerns that Nancy Olivieri had been treated badly and that the whole situation could become a public embarrassment,"² if efforts were not made to resolve matters.

Dr. Durie became interested in June 1997, shortly after Dr. Dick and independently, when he happened to meet Dr. Olivieri in a Hospital corridor. She appeared distressed and when he asked her why, she described the dispute and her concerns over lack of support from the Hospital and the University. He asked for all the documentation she had, and spent several weeks reviewing the material she provided. He then volunteered to intercede with the administrators.

At Dr. Durie's request, a meeting was held on September 11, 1997, attended by: Dean Aberman; HSC Executive members Drs. Goldbloom, O'Brodovich and Buchwald; and several clinical scientists, Dr. Zipursky (who had been a mentor of Dr. Olivieri), Dr. Zlotkin (the former REB Chair), Dr. Gallie, Dr. MacGregor, and Dr. Durie. The purpose of the meeting was to discuss concerns over the perceived lack of effective support for Dr. Olivieri and the principles involved in the dispute with Apotex. Dr. Durie told this Committee that Dean Aberman did not accept suggestions that the Hospital and the University could have done more to assist her. Dr. Durie's notes from the meeting recorded that Dean Aberman and the Hospital administrators "expressed the view that Dr. Olivieri's concerns had been handled fairly, objectively and with the full support of the respective institutions," and that they did not accept that there was a "need to conduct an independent review of events."³ Dr. Durie reported that he came away from the meeting with the conclusion that further attempts at an internal resolution would be futile.* He did not intercede again until March 1998, when he and others began to call for an independent inquiry.

Other than having attended the September 11, 1997 meeting with Dean Aberman and the HSC administrators, Dr. Gallie's first involvement came early in 1998. In January 1998 she was appointed Director of the Cancer and Blood Program in the HSC Research Institute, and thus the person to whom Dr. Olivieri reported in regard to research duties. She obtained from Dr. Olivieri a large quantity of documents in the spring of 1998, and said she was "astounded" by what she considered to be the gravity of the situation revealed by the documentary record. She felt a responsibility to try to resolve the difficulties between Dr. Olivieri and senior administrators arising from the Apotex dispute. On June 3, 1998 she wrote a letter to Dr. Buchwald and

*It is relevant to note that a week before the meeting of September 11, 1997, Dean Aberman met with Drs. Goldbloom, O'Brodovich and Buchwald to discuss communications to him from Dr. David Nathan and Sir David Weatherall. They had expressed concern that Dr. Olivieri "was not being adequately supported" by the University and the Hospital in connection with the actions by Apotex. (See sections 5N(3) and (4).) Dean Aberman had replied to the effect that the institutions "had supported Nancy." The four administrators "agreed that no further action is necessary at this time." (e-mail sent by Dean Aberman to HSC administrators, September 2, 1997, summarizing discussions.)

Mr. Strofolino, enclosing a chronological summary of events in the L1 trials and controversy she had drawn up. Her letter summarized the institutional concerns she saw, for instance:

Apotex, Inc. was supported in their interpretation that L1 was effective and safe by Dr. Gideon Koren, also an HSC senior scientist... Academic differences of opinion are normal and healthy when freely expressed; in this particular instance, the investigator suggesting lack of effectiveness and toxicity of L1 was threatened if she disclosed her data and interpretation, while the investigator reassuring safety published with the drug company.⁴

Dr. Gallie informed the administrators that they should anticipate media attention and public concern, once Dr. Olivieri's paper appeared in the *New England Journal of Medicine* (it was then in press). She continued:

I urge you to take these issues seriously. I can not imagine that any other item on your busy agendas can have greater importance. The public who donate to HSC understand that our Institution is a prime guardian of the safety of children. The clear issue here is HSC's approach to conflict of interest in human research. Does HSC defend the interests of patients and scientific integrity or do we acquiesce to the financial interests of research sponsors? It is imperative that, as senior officers of our institution, we act with dispatch to protect patient safety and research integrity.⁵

Dr. Buchwald replied to Dr. Gallie on June 10 with a letter of reassurance, to the effect that everything was well in hand.⁶

Dr. Chan, a research and clinical colleague of Dr. Gallie in oncology, became involved in the spring of 1998. She assisted Drs. Durie and Dick in organizing a petition from many staff to Dr. Buchwald in June 1998, calling for an external review of the controversy.⁷

Drs. Chan, Dick, Durie and Gallie said that they subsequently came to be regarded as not neutral, but rather as supporters of Dr. Olivieri. They felt that to act with integrity, they had to make a choice, and have since the summer of 1998 steadfastly supported Dr. Olivieri. Drs. Chan, Dick, Durie and Gallie each reported to this Committee that they encountered what they consider to be increasing hostility and workplace penalization by Hospital administrators because of their support for Dr. Olivieri. They stated that this treatment is documented through correspondence and through personal encounters which were witnessed by others. For instance, in mid-October 1998, Mr. Strofolino and HSC legal counsel Mr. William Carter ejected Drs. Gallie and Olivieri as they were entering a meeting of all senior scientists for which they had received notification to attend. This event occurred two days after Drs. Gallie, Chan, Durie and Olivieri had signed the "Participation Agreement" under which they would participate in the Naimark Review. In January 1999 the Hospital administration issued "gag orders" to Drs. Chan, Durie, Gallie and

Olivieri directing them not to discuss their concerns publicly (see section 5M). All four scientists consider that they have been unfairly treated in regard to significant employment matters, including salary, and have had to expend substantial personal resources to defend their rights and interests.

Drs. Chan, Dick, Durie and Gallie reported to this Committee that they consider that the managerial approach of the senior HSC administration is illustrated by the letter Dr. Gallie received from Dr. Buchwald on December 7, 1998. In this letter, Dr. Buchwald took Dr. Gallie to task for her conduct and attitude. Among other things, he rebuked her for publicly criticizing the Hospital administration's conduct and attitude in the L1 controversy:

We clearly have completely different views about your responsibilities as Program Head. You apparently believe that your moral duty overrides your accountability to me as Director of the Research Institute and to the formal leadership of this institution, including its Board.... We need to resolve the conundrum that we find ourselves in, both for our own sakes as well as for the institution. The choices are clear: since you believe that your conscience compels you to denigrate this institution and its leadership, then you cannot at the same time be part of that leadership.⁸

He concluded the letter by telling her that he was considering whether to remove her from her research program directorship. A week later, Dr. O'Brodovich initiated removal of Dr. Olivieri from her clinical program directorship, after her legal counsel had made a public remark critical of the Hospital (see section 5M).

(2) Fact-finding by Professor Rowell

Professor Mary Rowell was one of the two members of the Hospital's bioethics department, and also a member of the University's Joint Centre for Bioethics. She was a member of the Research Ethics Board (REB) when Dr. Olivieri brought to it her finding of the risk of loss of sustained efficacy of L1. She told this Committee that she is of the view that Dr. Olivieri's actions in that matter were entirely proper. She is also of the view that the authority of the REB was then at issue, because of the pressures Apotex was exerting, particularly on Dr. Zlotkin, its Chair. She said that Dr. Olivieri was under very great pressure during that period and did not appear to have the moral support of the HSC administration.

In June 1998, Professor Rowell was asked to intercede by Dr. Durie and she agreed to do so. She approached Dr. Buchwald, who suggested she undertake a review of the facts of the matter, as a preliminary step to a mediation process. Professor Rowell agreed and in discussions with Dr. Buchwald drew up terms of reference and a list of persons to interview. She was to report on facts and make suggestions on helpful courses of action from a bioethics perspective, with a view to getting "everyone around the same table" eventually. The list of persons she interviewed included several members of the Hospital Executive, and Drs. Olivieri, Chan, Dick, Durie and Gallie. Following the round of interviews, Professor Rowell concluded that mediation efforts would be futile. She told this Committee that she subsequently decided to offer support to Dr. Olivieri in the ethical stand she took on the need to inform trial participants of a risk.

(3) The petition for an inquiry

On June 26, 1998, Dr. Durie, Dr. Dick and many other HSC scientific and medical staff signed a petition to Dr. Buchwald concerning “the very troubling difficulties that have arisen between Dr. Olivieri and Apotex.”⁹ The petition stated that, “Those serving in positions of leadership and responsibility” had a number of “moral and ethical obligations” which were listed. The list included: protecting the rights and interests of research subjects in HSC studies; safeguarding the independence of investigators; and addressing potential institutional conflict of interest.

The petition also listed a number of matters which were cited as indicating potential conflict of interest. This list included: funding by Apotex for projects in HSC and the University of Toronto; the continuing use of laboratory space in HSC by an Apotex employee (an apparent reference to Apotex Vice-President Dr. Spino); “Apotex has actively supported HSC researchers who express a favourable opinion [on L1—an apparent reference to Dr. Koren], but strenuously discouraged, through legal threat, an individual with an unfavourable viewpoint [an apparent reference to Dr. Olivieri]; and the fact that “Neither HSC (nor the University of Toronto) have fully investigated this issue during a period of more than two years.” The petition concluded with a call for the establishment of “an external independent review of all matters concerning this case.”¹⁰

(4) The letters by Dr. Zlotkin, Dr. Corey, & Dr. Saunders

In the summer of 1998 Dr. Buchwald received letters from each of Drs. Zlotkin, Corey and Saunders. Dr. Stanley Zlotkin is a member of the Division of Gastroenterology and Nutrition in the Hospital and had served as Chair of the REB during the entire period of the Apotex-sponsored L1 trials. His letter raised two cases where external sponsors of research had tried to interfere improperly with research findings. One of these involved his own work and a foundation which funded it. The other was the case of Dr. Olivieri and Apotex. He explained that in the latter case, there were serious unresolved issues of institutional conflict of interest, as well as an unresolved issue regarding control and use of data between Dr. Olivieri and a previous collaborator (an apparent reference to Dr. Koren). Dr. Zlotkin continued:

Whether true or not, the fact that Apotex is actively supporting HSC researchers [an apparent reference to Dr. Koren, notably] who view favourably the outcomes of the research and discouraging, through legal threat, an individual with an unfavourable view, lends support to the view that the autonomy of Dr. Olivieri is at stake. This fact alone, should raise the ire of those who run the Institution.¹¹

Dr. Zlotkin concluded his letter with a call for “an external **independent** review.” (emphasis in original)

Dr. Mary Corey is an epidemiologist in the Hospital. She was one of the four persons contracted by Apotex to serve on its Expert Advisory Panel in July 1996. The panel disagreed with Dr. Olivieri’s finding that there was a risk of loss of sustained efficacy. However, two years later Dr. Corey informed Dr. Buchwald by letter that she now considered that Apotex had misled the EAP as to both facts and circumstances. In particular she wrote, “I believe the expert panel set up by Apotex may not have had all the information necessary to form unbiased conclusions.”¹² She was later interviewed by the *Globe and Mail* and reiterated her concern publicly, “we did not have the up-to-date data.”¹³ She told this Committee that Dr. Spino then called her and questioned her allegations. She replied to Dr. Spino that she had not been misquoted. In her letter to Dr. Buchwald she added that Dr. Olivieri should have been provided with institutional support.¹⁴

Dr. Fred Saunders, Director of the Bone Marrow Transplant Program in HSC, also wrote to Dr. Buchwald in July 1998. He informed Dr. Buchwald that he had recently signed a contract with a drug company that gave “the company complete control over a study... They can change the protocol at will and have veto power over all publications and presentations.”¹⁵ He added that this contract had been formally reviewed and approved by the Hospital. He proposed that there should be an institutional policy to prevent such “one-sided” arrangements. Thus it appears that even after the problem with Apotex emerged, the Hospital was in fact giving official approval to contracts with publication and other restrictions more sweeping than those in the LA-01 contract Dr. Olivieri signed in 1993.

(5) Support for the HSC administration

As support for the position of Dr. Olivieri grew and criticism of the administration for its perceived lack of action increased and became public, other staff expressed support for the administration. For instance, a majority of the division chiefs in the Department of Pediatrics, including Dr. Koren, wrote a group letter to the Chair of the Board:

We wish to express our unqualified support for Mr. Michael Strofolino and Drs. Hugh O’Brodivich, Manuel Buchwald and Alan Goldbloom in terms of their integrity, the legitimacy of the processes they have established and pursued recently in a [sic] attempt to resolve this matter, and their commitment to the care, health, welfare, and safety of children.¹⁶

(6) Criticism of Dr. Koren

In 1996, before and after Apotex terminated the L1 trials, Dr. Koren had given repeated assurances to Dr. Olivieri that he supported her position on the risk of loss of sustained efficacy. Apotex claimed that during the same period Dr. Koren supported its opposing position. In early 1997, Dr. Koren was listed as senior author of two abstracts co-authored with others funded or employed by Apotex submitted to a conference scheduled for April 1997 in Malta. Among the co-authors were research fellows of Dr. Koren who received salary support from Apotex funds granted to Dr. Koren after the trials were terminated. The abstracts used data from the LA-01 and LA-03 trials and reported that L1 was effective and safe—the position of Apotex. Dr. Olivieri learned of these abstracts only after they had been submitted (see section 5N).

Later in 1997 and in 1998, issues were raised regarding Dr. Koren's actions in these and other matters. In November 1997, Dr. Dick raised with Dr. Buchwald concerns about Dr. Koren's scientific and personal conduct toward Dr. Olivieri. On this basis he questioned the appropriateness of appointing Dr. Koren to a new administrative position in the Hospital's Research Institute.¹⁷

In late March 1998, Dr. Olivieri alleged that one of Dr. Koren's Apotex-funded research fellows, Dr. Orna Diav-Citrin was identified accessing the chart of a patient in the thalassemia clinic without authorization, and lodged complaints with the Hospital administration.¹⁸ For more than a year, there had been an ongoing dispute between Apotex and Dr. Olivieri over certain data on thalassemia patients who had been enrolled in L1 trials. On legal advice that she was not required to provide this data to Apotex, Dr. Olivieri had repeatedly refused to provide it, either directly to Apotex, or to Dr. Koren who had approached her on behalf of the company.¹⁹ Dr. Olivieri said that the clinic files contained research information that Apotex had been requesting. In a letter of complaint dated April 2, 1998 to Medical Advisory Committee Chair Dr. Laurence Becker, Dr. Olivieri reported that neither Dr. Diav-Citrin nor Dr. Koren had requested access, nor had they been given permission to access clinic charts.²⁰

Dr. Koren maintained that this was an innocuous matter. He wrote to Dr. Olivieri that Dr. Diav-Citrin was “summarizing a pharmacokinetics study... done under my guidance and supervision,” and that she had been seeking “to verify demographic data on a patient, in order to complete the above paper.”²¹ However, in a letter written a few weeks later, Dr. Koren said that if Dr. Diav-Citrin had consulted him in advance, he “would have advised her to approach Dr. Olivieri” to request access.²²

Dr. Moore, the REB Chair, expressed the view that there was no policy to prevent such access as had occurred in this case.²³ Following an

investigation, the HSC administration decided to take no action and relied on Dr. Moore's view in reaching this decision.²⁴

In her letter to Dr. Becker on April 2, Dr. Olivieri also outlined her wider dispute with Apotex, that began with the termination of the trials and the initial legal warnings on May 24, 1996, and was still ongoing. She added:

During this time, Dr. Koren has continued to assist Apotex in the development of deferiprone and to receive funding from Apotex Inc., including that for Dr. Diav-Citrin's salary.²⁵

Dr. Olivieri copied Dr. Koren on this letter, and he wrote to Dr. Becker in response on April 15, disputing Dr. Olivieri's allegation concerning his continuing assistance to Apotex. He wrote that Dr. Diav-Citrin's "study has nothing to do with Apotex," and that, "The funding we received [from Apotex] after the unplanned discontinuation of the trial... was not dependent on work related to deferiprone for thalassemia."²⁶ In a similar letter to Dr. Buchwald on May 7, Dr. Koren said that Dr. Olivieri's allegation constituted "serious slander [sic] and defamation against me."²⁷ Dr. Koren continued:

As indicated by me repeatedly, the incidence [sic] with Dr. Orna Diav-Citrin has nothing to do with Apotex. This paper was not done for Apotex and, in fact, it is very likely that Apotex will not like the results.

He added, "The only individual paid to assist Apotex in lisencing [sic] the drug is Dr. Olivieri herself." This was a reference to Dr. Olivieri's consulting contract to design and organize the LA-02 trial at international sites. However, Dr. Graham Sher (co-author with Dr. Koren of one of the two abstracts for the April 1997 conference in Malta) also had a consulting contract with Apotex for work on the LA-02 trial.²⁸ (See section 5N(5).)

A week after Dr. Koren wrote this letter to Dr. Buchwald, he and Dr. Diav-Citrin met with Drs. Spino and Tricta of Apotex "to discuss Orna's paper," as Dr. Koren's notes of the meeting record.²⁹ Dr. Olivieri learned much later that, on August 12, 1998, Dr. Koren, Dr. Diav-Citrin and another Apotex-funded research fellow had submitted an article to the journal *Therapeutic Drug Monitoring* on the efficacy of L1. It was published in 1999 and was based on LA-03 trial data.³⁰ The article did not disclose funding support by Apotex, did not note previously published findings of risks of L1, and did not acknowledge the contributions of Dr. Olivieri and others to generating the data on which it was based. (See section 5R.)

Dr. Koren's actions in regard to the Malta abstracts were criticized by Dr. Gallie in early June 1998, and were alluded to in the petition signed by Dr. Durie and others later that month. In mid-August 1998, following publication of Dr. Olivieri's article on risks of L1 in the *New England Journal of Medicine*, the controversy became the focus of widespread media

attention. At this time, Dr. Gallie was quoted in the press as having said that Dr. Koren's studies were "providing very economically useful information for the drug company [Apotex]. ... They've quoted him in two ways, to say that the drug is safe and that Dr. Olivieri's interpretation is wrong."³¹ Dr. Koren warned her of legal action, and in November 1998 filed an action for defamation against Dr. Gallie and two Toronto newspapers.³² However, at the time the present report was completed, the respondents had still not received notice of a date by which a defence should be filed.³³

(7) HSC & a major University-Apotex project

Beginning in 1991, Apotex and the University of Toronto were negotiating about a multimillion dollar donation by the company, and had reached agreement in principle in the spring of 1998 (see section 4). On June 11, 1998 University Vice-President Mr. Jon Dellandrea convened a meeting with the foundations of several of the University's affiliated teaching hospitals, including HSC, to discuss the proposal and possible participation by hospitals:

Jon opened the meeting indicating he was "the messenger for a donor who, if the deal closed, would be the largest donor to U of T, and the lead gift to its campaign."³⁴

The foundation representatives were advised that "the donor wished to remain anonymous during the negotiations" with the hospital foundations. By this date, the dispute involving Apotex and Dr. Olivieri was becoming more widely known, and was anticipated to become the subject of media attention. The HSC foundation indicated it would require the identity of the donor in advance and was advised a week later that it was Apotex. In a memo to the Naimark Review, Ms. Dianne Lister, President and CEO of the HSC Foundation, described subsequent discussions:

Being aware of some difficulties emerging with Apotex and Dr. Olivieri, I discussed the issues with [HSC President] Mike Strofolino and Dr. Buchwald. On behalf of the HSC Executive, they agreed that it would be inappropriate to be perceived to be at any stage of negotiations with this prospective donor.³⁵

On June 25, 1998 Ms. Lister advised Mr. Dellandrea, "we are unable to participate in this proposal."³⁶

(8) HSC publicly repeats Apotex's allegations

In licencing submissions for L1 to regulatory agencies in early 1998, Apotex stated that the "primary reason" it had terminated the Toronto efficacy and safety trials was that, allegedly, Dr. Olivieri had committed such severe protocol violations that the data was compromised.³⁷ (In 1996 and 1997 the company had given a different reason—see section 5F). Apotex had earlier

made this allegation informally to Dr. Buchwald, as noted in the Naimark Report:

During the early part of 1998, at a meeting of the Toronto Biotechnology Association, Dr. Spino approached Dr. Buchwald and stated that the L1 trial under Dr. Olivieri's supervision had a number of protocol violations that was an order of magnitude greater than any of the other trials they were funding. Dr. Buchwald expressed surprise and indicated to Dr. Spino that he would not *investigate* such an allegation unless Dr. Spino put it in writing. There was no further word from Dr. Spino or Apotex on this subject until it was mentioned in a letter to Mr. Strofolino from Dr. Spino dated August 31, 1998.³⁸ (emphasis added)

Dr. Spino's lengthy letter to Mr. Strofolino of August 31, 1998 said:

We took positive action to terminate the trials at HSC on the basis of the protocol violations and other serious matters outlined in this letter.³⁹ *

Thus, HSC now had the allegation in writing, which Dr. Buchwald said would be needed before he would "investigate" it. However, neither Dr. Buchwald nor any other member of the HSC Executive investigated the allegation. Instead, the next day, September 1, 1998, the Executive sent out an e-mail statement on the L1 controversy to all HSC medical and scientific staff in which it repeated Apotex's allegation. The Executive's statement included the following:

Dr. Olivieri... expressed her concerns [about the risk of loss of sustained efficacy] to Apotex and the HSC Research Ethics Board. The REB recommended that she change the patient consent form to reflect this new information. This she did... Both Apotex and other scientists involved in the L1 trials disagreed with Dr. Olivieri's interpretation of the data. Apotex also expressed concerns to Dr. Olivieri about protocol violations during the course of the study. As a result, Apotex cancelled the clinical trial on May 24, 1996.⁴⁰

The allegation, simply put, was to the effect that Dr. Olivieri was not a very diligent scientist, and had allowed so many protocol violations that this was one of the main reasons Apotex terminated the trials. This late-arising allegation was a serious one, and one potentially damaging to Dr. Olivieri's distinguished international reputation. It was made privately in a letter to the HSC President, by a for-profit drug company that had been using legal warnings to deter Dr. Olivieri, one of the Hospital's medical staff, from informing the Hospital's patients of a risk. Yet the Hospital's Executive, without investigating it, indeed without even asking Dr. Olivieri for her position on the allegation, repeated it in a statement issued to a large number of individuals. The Executive's statement subsequently was forwarded to

*Among the "other serious matters outlined" in Dr. Spino's letter was that Dr. Olivieri "lacked objectivity" in reporting to the Research Ethics Board that she had identified an unexpected risk of Apotex's drug.

many others outside HSC by a person supportive of the Executive in the L1 controversy, Dr. Sergio Grinstein.⁴¹

Dr. Olivieri responded to the Executive's statement on September 5, in a lengthy memo addressed to University Provost Dr. Adel Sedra and HSC Board members, that she copied to others. She outlined her position on the entire controversy and questioned the process whereby allegations she had not seen were publicly repeated with no notice to her or opportunity to review the specifics.⁴² Dr. Olivieri was not provided with an opportunity to review and respond to the details of Apotex's allegations of protocol violations until 2000, when a court of the European Communities allowed an application she filed to proceed. As the present report was completed, matters were still before the court (see section 5U).

(9) Conclusions

1 | HSC administrators and Dean Aberman did not agree with concerns expressed by several Senior Scientists that the Hospital and the University had not provided effective support to Dr. Olivieri in the dispute with Apotex. The administrators' responses gave rise to more widespread concerns in the Hospital and, eventually, demands for an independent external inquiry.

2 | During 1997 and 1998 Drs. Dick, Durie, Gallie and Chan took the initiative in calling for effective support for Dr. Olivieri in the dispute with Apotex and in subsequent disputes with the HSC administration. They have since been regarded as Dr. Olivieri's principal supporters in the L1 controversy. They have been criticized and, in their view, penalized, by HSC administrators for their outspoken defence of Dr. Olivieri and the principles of academic freedom and ethical conduct of research.

3 | The L1 dispute became a highly public matter in August 1998, two years after it began in May 1996. Dr. Dick in November 1997 and Dr. Gallie in June 1998 had alerted the Hospital administration to the possibility this could occur.

4 | Dr. Olivieri and several colleagues alleged that Dr. Koren was in a conflict of interest, and he then alleged that Dr. Olivieri was in a conflict of interest. Whenever a university faculty member accepts research funding from a commercial sponsor to work on development of a product or process owned by that sponsor, there is potential for conflict of interest to arise. The potential may be increased where the faculty member also signs a personal services (consulting) contract with the same sponsor, as Dr. Olivieri had in this case. Such potential conflicts of interest are common and may be resolved or managed in various ways.

Dr. Olivieri defied the sponsor's wishes when she moved to inform patients of a risk of Apotex's drug she identified, and the company immediately terminated her consulting contract for the international trial (LA-02), the same day it terminated the Toronto trials (LA-01 and LA-03). Thereafter she no longer had a potential conflict of interest.

Dr. Koren did not resolve his potential conflict of interest. Instead, potential became actual when he published work supporting Apotex's view that L1 was effective and safe, but failed to disclose in the publications the research funding he received from the company. His failure in this regard was significant in view of the very large amount of research funding he had received from Apotex in the years 1993–1997. (See sections 5G(3) and 5R.)

5 | In late June 1998, the Hospital and the HSC Foundation declined to participate in a major donation to the University and some of its teaching hospitals by Apotex. This multimillion dollar donation had been under discussion since 1991. In declining participation, the Hospital said that the dispute between Apotex and Dr. Olivieri made it “inappropriate to be perceived to be at any stage of negotiations with this prospective donor.”

6 | It was improper for the Hospital Executive to have repeated publicly allegations made privately by Apotex against Dr. Olivieri’s work, without investigation or even consultation with Dr. Olivieri. This was damaging to her reputation and had the effect of serving Apotex’s interests.

5M | Removal of Dr. Olivieri as Program Director

(1) Proposed decentralization of the SCD program

THIS SECTION describes interactions between the HSC administration and Dr. Olivieri occurring contemporaneously with the Apotex dispute that may have had a bearing on how the HSC leadership dealt with that dispute.

During the period 1986–1998, the patient load in Dr. Olivieri’s hemoglobinopathy programs grew from approximately 150 to 450 patients (100 patients with thalassemia and 350 with sickle cell disease—SCD). The growth in numbers of patients in the Toronto area was a reflection of Canada’s changing immigration patterns in recent decades.¹ The greater numbers of patients needing the specialized care required to manage these potentially fatal genetic diseases placed increasing demands on resources at a time when funding was being eroded by governments.

In the mid–1990s the Hospital for Sick Children undertook to develop a pediatric network involving other hospitals in Metropolitan Toronto for provision of inpatient and outpatient care to patients with certain diseases. In 1995 Dr. Olivieri was informed that the HSC administration had selected the SCD program she directed as one of several programs to be decentralized (or “satellited”) to regional hospitals. She questioned the decentralization of the SCD program on medical, administrative and scientific grounds,² and the proposal was not strongly pursued for some months. The matter was complicated administratively by the fact that when SCD patients reached adulthood, their care was provided in the The Toronto Hospital (TTH) located across the street from HSC. The TTH administration appears not to have been persuaded that decentralization of SCD care was necessarily the best approach.

In early 1996 Dr. Olivieri discussed her concerns with HSC President Mr. Michael Strofolino and TTH Physician-in-Chief Dr. Michael Baker, and informed Dr. Melvin Freedman (HSC Chief of Hematology) that she would “continue to negotiate directly” with them.³ This led to a meeting in April 1996 of HSC Vice-President Dr. Alan Goldbloom, HSC Research Institute Director Dr. Manuel Buchwald, incoming Pediatrician-in-chief Dr. O’Brodivich, and Dr. Olivieri. They discussed the decentralization proposal, Dr. Olivieri’s concerns over it and over inadequate resources for existing programs, and the administrators’ concerns over what they considered end runs by her. Dr. Olivieri was advised she should work with her division head Dr. Freedman, but Dr. O’Brodivich “indicated he would be prepared to address some of these issues [she had raised].”⁴ It is clear from the documentary record of these interactions in the spring of 1996 that some HSC administrators considered Dr. Olivieri to be a difficult subordinate,

uncooperative with management directives, while she considered them to be unreasonable, hence not deserving of deference.

In early May 1996 Dr. Freedman advised Dr. Olivieri that HSC now intended to proceed with the decentralization, and she replied that her concerns remained.⁵ Strongly worded correspondence between Dr. Olivieri and several administrators was exchanged then and over the ensuing months. For instance, Dr. Freedman wrote to Dr. Olivieri on May 10, 1996 indicating that the decision to decentralize the SCD program was firm and that it was based on resource needs. “[T]here are, once again, very strong directives from the Department of Paediatrics, with firm endorsement from the Executive Office that we contain the progressive growth of the Sickle Cell Clinic” and resulting increases in costs. He added, “The obvious benefit of this type of arrangement is that it alleviates you and our clinic of direct clinical responsibility yet allows you to get the research data that you want.”⁶ Dr. Olivieri replied at length on May 13, noting that the concerns she raised the year before had not been addressed, and explaining to Dr. Freedman why she considered his claim of “obvious benefit” not to be well founded.

The medical reason Dr. Olivieri gave for opposing decentralization was that two decades of research at clinical centres in the USA had demonstrated that morbidity and mortality in SCD patients were significantly reduced where care was provided in tertiary hospitals by experienced hematologists.⁷ In May 1996, as in February 1995, she asked for assurances that the quality of patient care would remain high under the proposed new arrangement,⁸ but was not reassured by the responses she received. A year and a half later, after much discussion and controversy, the same concern remained and appeared to be shared by medical administrators in The Toronto Hospital where adult SCD patients received their care. In October 1997 when the controversy over decentralization of the HSC program was reported in *The Medical Post*, Dr. Armand Keating, Director of the Division of Hematology in the University of Toronto and in The Toronto Hospital, was quoted as stating:

In principle, we’re very much in favour of decentralizing a lot of activity done on University Avenue (Sick Kids) that can be done in the periphery, but there must be assurance that adequate delivery of care can be provided, and I’m uncertain that would be the case in this [SCD] satellite endeavour.⁹

The research reason that Dr. Olivieri gave for opposing decentralization was that it would be more difficult and time-consuming to supervise clinical research trials and ensure high standards, if patients were in widely separated locations. She noted that she had just received a Scientist Award from MRC, which provided five years of salary support to enable her to

⁹Leading American authorities on clinical management of SCD make this point, for instance Dr. Elliot Vichinsky of the Children’s Hospital, Oakland (see endnote).

concentrate on research. Such awards are made on the basis of the scientist's distinguished record, and on condition that her employer ensured that she has substantial protected time from administrative and clinical duties to devote to research.¹⁰ Dr. Olivieri also said that the proposed decentralization could jeopardize an opportunity for HSC and TTH to participate in a planned multi-centre study for improving treatment of SCD patients that could attract substantial funding from the USA National Institutes of Health (NIH). She added that Dr. Keating shared her concern. She reviewed program budget details and suggested alternative arrangements.

In her May 13 reply to Dr. Freedman, Dr. Olivieri also wrote that, "such marginalization of services to an almost exclusively black population is a delicate issue. It is difficult to see how the Hospital's Executive could justify to Toronto's black community the policy of moving children with sickle cell disease *away from the province's only Comprehensive Care Program.*"¹¹ (SCD occurs predominantly in black populations.) She concluded by suggesting that no decision should be made until Dr. Haslam's successor as Pediatrician-in-Chief, Dr. O'Brodovich assumed office in July. However, the administration's position on the SCD program decentralization did not change, and disagreements over this proposal between Dr. Olivieri and Drs. Goldbloom and O'Brodovich escalated during the next several months. In October 1996, Dr. Goldbloom wrote:

I stated to you that if you were unable to cooperate with this arrangement, then the clinical directorship of the haemoglobinopathy program would be assigned to someone else.¹²

In these circumstances, without adequate labour relations grievance procedures for clinical scientists,¹³ Dr. Olivieri sought advice from private legal counsel and so informed the Hospital.¹⁴

It was around this time in the fall of 1996 that spokespersons for SCD patient support groups became active, writing to leading medical experts on SCD in the United States for opinions on management of care for SCD patients, and requesting that Dr. O'Brodovich meet with them to hear their concerns.¹⁵ The requested meeting occurred in January 1997. The SCD community representatives then wrote to the Hospital administrators that the meeting had failed to dispel their concerns.¹⁶ Upon receipt of this letter from the community representatives, Dr. O'Brodovich drafted a reply. He then wrote to Dr. Olivieri and asked her to co-sign with Dr. Goldbloom and him the draft letter to the community group, "as it would indicate that this is a united approach."¹⁷ She again sought legal advice and wrote to Dr. O'Brodovich to inform him that she could not, "in personal conscience, affix

[her] signature to [his] letter.”¹⁸ Dr. Olivieri’s refusal to co-sign the letter drafted by Dr. O’Brodivich is dated February 19, 1997.*

The letter Dr. Olivieri refused to co-sign was sent to the patient support group by Drs. O’Brodivich and Goldbloom on February 25. The letter indicated that HSC had done no detailed studies to determine whether the SCD resource problem could be solved by the proposed decentralization. It continued:

The fact is that costs are, at this point, a secondary issue. Our overriding purpose, as documented both in our own strategic plan and in the recommendations of the Metro District Health Council Restructuring Commission is the establishment of a Child Health Network involving regional paediatric centres. ... The fact is that no formal financial plans or budget plans have yet been developed with relationship to any of our new network initiatives¹⁹

The letter put forward a new reason for selecting the SCD program as one of those to be decentralized, namely, convenience to patients:

[T]he initiatives are being proposed because we believe we can provide care closer to the home community for many patients, at a standard that we have been providing at The Hospital for Sick Children.²⁰

This justification was not well appreciated by the SCD community. In a “Facts Sheet” distributed in response, the SCD support group said that, “This disease... requires management in a *tertiary setting*,” and that in fact the proposed satellite location, the Scarborough Centenary Health Centre, was not conveniently located for a large majority of SCD patients.²¹

In summary, the first justification (resources) advanced for selecting the SCD program for decentralization was not sustained by those who had put it forward, and the second (patient convenience) was rejected by the group representing the community that it was supposed to benefit. This left an impression with Dr. Olivieri and the patient support group that the selection of the SCD program was not well considered by the HSC administration. Subsequently, Mr. Antoni Shelton, Executive Director of the Urban Alliance on Race Relations, wrote a letter of protest to the HSC Board of Trustees. He said that, “this decision, if allowed to be implemented, will be harmful to many families and individuals in the Black community,” and asked that the initiative be “stopped,” because “no adequate justification” had been provided.²²

*February 19, 1997 was the same day that Dr. O’Brodivich confronted Dr. Olivieri with the allegation that she had failed to inform the relevant authorities (the REB and himself) about her identification of the risk that Apotex’s drug LI could cause chronic liver toxicity. (See sections 5K, 5O and 5P.)

Drs. Goldbloom and O’Brodivich were displeased with what they saw as Dr. Olivieri’s uncooperativeness, warning her that she could be relieved of her program directorship. However, confidence in her ability and judgment was undiminished in The Toronto Hospital and in January 1997 she was appointed director of its Hemoglobinopathy Program. For two years she held the position of Program Director in both HSC and TTH.

Discussions concerning the proposed decentralization of HSC’s SCD program to Scarborough were resumed in the summer of 1997. In August, Dr. Olivieri wrote to Dr. Freedman to reiterate her original concerns over resources, including the additional resources she felt would be required to ensure that equivalent care could be provided at the satellite location. She noted that a similar proposal to satellite oncology care included provision for additional financial support, in contrast to the proposal to satellite SCD care. She also noted that Drs. Baker and Keating were providing additional resources for the SCD program at TTH with a view to keeping care of adult SCD patients centralized there, since TTH had decided the opposite of what HSC had been proposing.²³ The satellitization issue at HSC again subsided, only to re-emerge in early 1999, as we discuss in subsection (3).

(2) HSC’s removal of Dr. Olivieri from her directorship & “gag orders”

Throughout most of 1998 Dr. Olivieri raised concerns over lack of program resources, first with HSC,²⁴ later with Dean Aberman,²⁵ again with HSC, then through legal counsel,²⁶ and finally in December, publicly, also through legal counsel. The frequency of her requests for clinical resources increased in the second half of 1998, following a reduction in July in the weekly hours clinical assistants would be available to see patients in the HSC hemoglobinopathy clinic. In extensive correspondence between Dr. Olivieri and Dr. Victor Blanchette, Chief of Hematology and Oncology, she expressed concerns that patients should obtain proper care and that, in the absence of adequate clinical support, she had to spend more time in clinical work than permitted in the standard arrangement between MRC and her employer for her Scientist award.²⁷ That arrangement required her to “devote at least 75% of [her] time to research.”²⁸

The disagreements over resources intensified during the same period that the L1 dispute became the subject of intense media attention, and the Naimark Review was in progress. In December 1998 two actions were taken that were viewed as sharp escalations in conflict by one party or the other. On December 9, the day the Naimark Report was released, the HSC Board of Trustees passed a resolution stating that Dr. Olivieri had “failed” in a report-

ing obligation, and referring the matter to the Medical Advisory Committee, the body that advises the Board on disciplinary action. The Hospital announced this action to the press.²⁹ (See section 5P.) On December 10, Mr. Clayton Ruby and Ms. Beth Symes, counsel for Dr. Olivieri, wrote a letter to the Hospital administration outlining Dr. Olivieri's concerns over program resources, and held a press conference to discuss the letter's concerns, at which Dr. Olivieri was not present.

On Sunday, December 13 the *Toronto Sun* reported on the press conference and on the Hospital's response. The *Sun* noted two statements made in the press conference: (i) in July 1998, availability of physician assistants for the HSC hemoglobinopathy clinic had been significantly reduced and this placed the health of children with potentially fatal diseases at greater risk; and (ii) "Children at risk include 350 sickle cell anemia patients, most of whom are black with sole-support mothers, and 100 thalassemia patients, 'none of northern European ancestry,' Ruby said."³⁰ The *Sun* quoted Ms. Cyndy DeGiusti, a spokesperson for the Hospital, as responding that, "This is a serious charge and we will be investigating," and that, to this end, "[HSC President Mr.] Strofolino sent the letter on to medical advisory and patient care committees." The newspaper quoted Ms. Symes as suggesting that the Hospital's removal of resources from Dr. Olivieri's program was "linked" to the L1 dispute involving Dr. Olivieri and Apotex. It also quoted the Hospital spokesperson as saying that "the Apotex battle may be Olivieri's motivation for her allegation of understaffing," and that, "there have been no complaints recently via normal channels." This is a surprising, as well as incorrect, statement in view of the extensive correspondence from Dr. Olivieri to Dr. Blanchette and others during the preceding months on this issue.

No information is available on conclusions reached by the "medical advisory and patient care committees" in their investigation of the concerns raised by Mr. Ruby and Ms. Symes. However, on December 16, before these investigations were completed, action of another kind was taken, when the Combined Chiefs' Meeting in the Department of Pediatrics was held that morning. The minutes record that the Chair, Dr. O'Brodovich, tabled the December 10 letter from Mr. Ruby and Ms. Symes, and the December 13 *Sun* article. The minutes also record that, "Dr. O'Brodovich and Dr. R. Laxer [Associate Chair] reviewed the current process by the Patient Care Committee which is underway to investigate these allegations." A motion was then passed, recommending to the Chair "that Dr. Olivieri be replaced by an acting medical director of the Hemoglobinopathy Program."³¹ The recorded preamble to this motion said that the implication of the statements by Dr. Olivieri's counsel was considered to be that the Hospital "would condone differential access to treatment ... based on racial and ethnic

origin.” The preamble added that the motion was put, “In the interest of patient care at the HSC and the reputation and integrity of the HSC.” The minutes record that all present supported the motion, including Dr. Koren. Dr. Olivieri did not learn of this meeting until January, when Dr. O’Brodivich implemented the Combined Chiefs’ recommendation.

On January 4, 1999, the University was advised by the Hospital that it planned to remove Dr. Olivieri from the position of Director of the Hemoglobinopathy Program. Events were described in a letter from the University Provost, Dr. Adel Sedra, to the Faculty Association President, Professor William Graham, on January 12:

The President of the University was advised by the Dean on Monday, January 4, 1999 that Dr. O’Brodivich had advised him that the HSC was planning to remove Dr. Olivieri from her administrative responsibility for the clinical programme... *President Prichard expressed objection to the process being suggested.* He advised that Hospital representatives should meet with Dr. Olivieri to put their concerns related to her performance of her administrative duties to her with her lawyer present and give her an opportunity to respond before any final decision was made.³² (emphasis added)

President Prichard’s objection was conveyed to the Hospital, which brought a telephone call from Hospital President Strofolino later that day. Provost Sedra’s letter continued:

President Prichard, in this conversation, sought and received assurances from Mr. Strofolino that the proposed action would not impair her academic rights including her ability to conduct her research. (emphasis added)

In this telephone conversation on January 4, President Prichard, a former Dean of Law, explained to Mr. Strofolino the importance of due process and advised how it could be provided, as the Provost’s letter described:

With respect to process, Mr. Strofolino indicated that the HSC planned to deliver a letter to Dr. Olivieri advising her that she had been removed from the position of Programme Director. *President Prichard in unequivocal terms criticized the process suggested by Mr. Strofolino.* President Prichard’s position was that the process proposed was not collegial and not appropriate in an academic environment. President Prichard advised Mr. Strofolino to have a meeting with Dr. Olivieri before a final decision was made, to invite Dr. Olivieri’s lawyers to attend the meeting and to ensure that Dr. Olivieri understood the concerns of the HSC and that she be given an opportunity to respond. *He stated that in the absence of such a process, the University could not support the Hospital’s decision.* (emphasis added)

However, two days later, on January 6:

The President of the University was advised that a meeting with Dr. Olivieri and her counsel was going to take place that afternoon. As a result, President

Prichard *believed* that the HSC was following the process suggested by him and was going to meet Dr. Olivieri prior to the final decision being made.

The President was very surprised to learn from the University's counsel (who was called by Dr. Olivieri's counsel) on Wednesday evening (January 6th) that Dr. Olivieri had been removed from her position as Programme Director by the Hospital for Sick Children and that the meeting had been limited to the delivery of the letter removing her from her administrative responsibilities. (emphasis added)

On January 6, 1999, when Dr. O'Brodovich presented the letter (co-signed by Dr. Blanchette) to Dr. Olivieri informing her she had been removed from her directorship,³³ he also presented her with a second letter. This second letter, co-signed by Dr. Buchwald, has been referred to in University documents as a "gag order."³⁴ It reprimanded her for criticizing the Hospital in public "in relation to the L1/Apotex matter" and directed her to comply with Hospital policy on communication with the public.³⁵ Letters with content identical to this second one were also addressed to Drs. Chan, Durie and Gallie.^{36*} While the University was informed in advance of the action to remove Dr. Olivieri from her administrative position, the University was *not* given advance notice of these "gag orders," as the minutes of the January 21 meeting of the Academic Board confirmed:

The President said the Hospital had given the University no notice of these letters. The colleagues had immediately ignored the notice and he understood and supported this action. Such orders had no place in a University.³⁷

In summary, the inappropriateness of the letters infringing the academic freedom of Drs. Olivieri, Chan, Durie and Gallie, and of the lack of due process in the removal of Dr. Olivieri from her directorship, was such that the University, for the first time since the L1 controversy began in May 1996, openly criticized the Hospital.

(3) HSC's justification of its removal of Dr. Olivieri

In their January 6 removal letter to Dr. Olivieri, Drs. O'Brodovich and Blanchette wrote that she had "failed to meet our expectations of a Programme Director."³⁸ The letter contained a list of ten allegations as comprising the basis for the decision, with various failures to perform administrative duties or to comply with directives being alleged. Interestingly, the letter contained no mention whatever of the motion in the Combined Chiefs' Meeting of December 16, which the action to remove Dr. Olivieri from the directorship implemented. However, the letter did mention the public statements of counsel Ruby and Symes (the basis for the Combined Chiefs' motion), as an adjunct to the eighth allegation in the series of ten.

*Dr. Dick, who was on sick leave at the time, was not sent a "gag order."

It is worth noting that the public remarks by counsel for Dr. Olivieri—about the substantial reduction clinic staff and the composition of the SCD and thalassemia patient populations—were statements of fact. It was not in dispute that physician availability for the HSC clinic had been reduced in July—in fact the reduction was acknowledged in the January 6 removal letter. Also, counsel’s statement about the composition of the SCD and thalassemia patient populations were facts well known in medical circles, and the concerns expressed were not new to Dr. O’Brodivich and other members of the HSC administration. It had been brought repeatedly to the attention of HSC administrators that, whatever their intentions, there was a possibility that the patient community would react adversely to significant changes in the system for delivery of care for patients with this very serious disease. Questions had already been asked as to why SCD was selected for a change to a system very different from proven programs at major American centres, and why the program for hemophilia, which affected other populations, had not been selected for satellitization. Dr. Olivieri, SCD patient support groups and the Urban Alliance for Race Relations had made such points several times.³⁹

The disputes over resources were prominent among the allegations in the January 6 removal letter, including the proposal to satellite the SCD program. Some allegations were obviously incorrect. For instance, allegation 8 said that Dr. Olivieri had been “passive” in response to the removal of medical staff resources that had occurred in July 1998. The extensive correspondence between Dr. Olivieri and Dr. Blanchette extending from July to November, followed by her engagement of Mr. Ruby who wrote on her behalf, demonstrates that her response was anything but passive.* Allegation 10 characterized her opposition to decentralization of the SCD program as “personal.” However, since 1995 she had been providing in writing well documented medical reasons as to why she thought decentralization of a treatment program for this disease was inappropriate, along with research reasons.

Dr. Olivieri might have effectively responded to the other allegations, as well, had she been given an opportunity. However, she was not given any opportunity, as President Prichard noted. In addition, the removal action was premature: it resulted from the motion by the Combined Chiefs on December 16 recommending removal to Dr. O’Brodivich—a motion passed before the investigation into her concerns had been completed, as the minutes recorded.

A detailed examination of the allegations on which the summary removal was based is unnecessary, because of two subsequent events in January 1999.

*The Naimark Report, published a month before Dr. O’Brodivich wrote the removal letter, found that during this period and on these resource issues, “Dr. Olivieri ..., as the record shows, was diligent in pursuing promptly matters of importance to her.” (Naimark Report, p. 105)

First, Dr. Olivieri reported to us that two days after she was removed as Director of the Hemoglobinopathy Program, she was summoned to meet with Dr. Blanchette. He asked her to continue in her duties, because no one with her level of expertise was available to replace her. Dr. Olivieri said that, in her view, Dr. Blanchette had asked her to accept medical responsibility for the patients, but without either the administrative authority or the title of Director. She considered this request unreasonable, except in the short-term, pending an appeal through the University. Second, matters related to the removal and the “gag orders” were resolved by an agreement signed by the Hospital, the University and Dr. Olivieri on January 25. Among other things, that agreement nullified the practical effect of the removal: “full responsibility and authority” over clinical care and clinical research in hemoglobinopathies in HSC were restored to Dr. Olivieri, but without the title of Director. Under the agreement, the title “disappeared” and “no similar title” was created.⁴⁰ Also, the Hospital “withdrew” the “gag orders.” (See section 5N.)

The January 25 agreement came about after interventions by distinguished scientists from abroad, legal counsel for Dr. Olivieri, the University of Toronto Faculty Association, the Canadian Association of University Teachers and President Prichard. Their interventions were motivated by the fact that her removal from the clinical and administrative authority as Director would mean the end of her clinical research programs in Toronto. Sir David Weatherall of the University of Oxford made this point to President Prichard in a letter dated January 8, two days after the removal:

This [removal] has come as a major blow to those of us who work in this research field and I doubt if some of you in Toronto appreciate its significance.... Dr. Olivieri’s programme, to many of us who have worked in the field for a long time, is probably the strongest internationally. This is because of your huge immigrant population from so many different developing countries. You have the numbers of patients and diversity of their different forms of haemoglobin disorder which is simply second to none. It is very difficult to do a lot of this work in the developing world, as I know better than most, and to lose the haemoglobinopathy programme [in Toronto] is a disaster for the field. There are very few talented scientists doing this kind of work and it is difficult to see who would take her place.... I have to emphasize... that this is what is going to happen unless steps are taken to rectify the matter, and quickly.⁴¹ *

*The hemoglobinopathies, SCD and the thalassemia syndromes, have played an important role in the development of the science of human genetics and of molecular medicine during the past half century. The advances in science have depended on advances in clinical research, and conversely. A popular account can be found in the book, *Genes, Blood and Courage*, by David G. Nathan (1995).

(4) Conclusions

1 | The number of patients in Dr. Olivieri’s clinical program tripled over the course of a decade, resulting in the need for increased resources. This occurred because of the growth in the number of persons in the Toronto area with the diseases in which she is a leading expert.

2 | The concerns over resources, and strong disagreements over possible courses of action, began before the dispute between Dr. Olivieri and Apotex erupted, and also before Dr. O’Brodivich succeeded Dr. Haslam as Pediatrician-in-chief. However, the disagreements intensified after these two events. Spokespersons for the Hospital and for Dr. Olivieri each linked the program resource dispute and the L1/Apotex dispute.

Although there was no express mention of Apotex in the January 6, 1999 removal letter, the Hospital had dealt with months of adverse publicity over allegations it had failed to defend Dr. Olivieri against Apotex. It is clear that this was part of the context of the removal, because in the “gag order” letters Dr. O’Brodivich and his administrative colleagues issued the same day, they said that these orders were being issued following “efforts to discredit the Hospital leadership, thereby undermining public confidence in the Hospital,” in relation to “the L1/Apotex matter.”⁴² The Naimark Report speculated that the lack of action by the Hospital administration in response to the continuing Apotex legal warnings to Dr. Olivieri in 1996–1997, “may perhaps be explained by the fact that... Drs. Olivieri, Goldbloom and O’Brodivich were intensely involved in... disagreements about the decentralization of the Sickle Cell Disease Program.”⁴³

3 | The HSC administration acted improperly in removing Dr. Olivieri from her directorship without due process.

4 | The Hospital’s removal of Dr. Olivieri was premature, since the investigation into Dr. Olivieri’s concerns (that HSC had publicly announced—see *Toronto Sun*, December 13, 1998) had not been completed.

5 | The removal of Dr. Olivieri was done summarily. When due process has been denied, we cannot know with certainty whether the accused person would have been able to answer all of the allegations. However, several facts lead us to conclude that it is likely Dr. Olivieri could have answered them:

- a) the denial of due process by HSC was deliberate and against the advice of President Prichard of the University, who had explained to the Hospital on January 4, 1999 that it was improper;

- b) there are parallels between Dr. O’Brodivich’s actions in this matter and his actions in placing incorrect information about Dr. Olivieri before the Naimark Review and before the Medical Advisory Committee (MAC). In both instances, the information he put forward was not disclosed to Dr. Olivieri and there was a failure to provide due process. Dr. O’Brodivich’s letter to the MAC inquiry into Dr. Olivieri’s conduct was dated January 4, 1999, only two days before his removal letter and “gag order” letters were written;
- c) the three-party agreement of January 25, 1999 restored Dr. Olivieri’s medical authority over the HSC hemoglobinopathy program.

7 | The HSC administration acted improperly in issuing the “gag orders” to Drs. Olivieri, Chan, Durie and Gallie. However, under the January 25 settlement, HSC withdrew the “gag orders” and undertook not to infringe academic freedom in future.

8 | The HSC administrators did not put forward cogent reasons for selecting the SCD program, among other possibilities, for decentralization. The administrators of The Toronto Hospital decided that their SCD program should not be decentralized.

9 | Some regard Dr. Olivieri as a demanding and difficult person to work with, and it appears that the relationship between her and Drs. O’Brodivich and Blanchette had become dysfunctional. However, her relationship with their counterparts in The Toronto Hospital, Drs. Baker and Keating, was good.* Her actions in the disagreements with the HSC administration over resources were in what she considered to be in the best interests of her patients, and to preserve her nationally and internationally respected research programs, and she gave reasons for her views. The agreement of January 25, 1999 resolved the administrative dysfunctionality by altering her reporting relationships—she would report to Dr. Baker for her work in HSC, and he would report on her work to Dr. Blanchette.

10 | The lack of effective dispute resolution processes for HSC medical and scientific staff contributed to the development of a situation in which clinical demands on Dr. Olivieri’s time were in serious conflict with the conditions for release time resulting from her Scientist Award, and in which her concerns about this went unresolved. Dr. Olivieri reasonably felt that she

*Dr. Baker, the TTH Physician-in-chief and Associate Chair of the University’s Department of Medicine, told this Committee of Inquiry that, although some viewed Dr. Olivieri as “difficult,” he would be pleased to have many more clinician-scientists “like her” in his hospital and department.

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had no recourse but to engage private legal counsel in an effort to resolve them.

5N | Events at the University of Toronto

(1) Academic Freedom

IN THE FALL OF 1998, the University issued statements on the L1 controversy that stressed the importance of academic freedom and the institution's obligation to protect it. In a twelve-point statement dated December 3, 1998, the University said:

As a faculty member of the University of Toronto, Dr. Olivieri is entitled to the full freedoms, rights and privileges of all members of the faculty including vigilant protection of her academic freedom.¹

On December 9, 1998, the day the Naimark Report was publicly released, University President Robert Prichard said:

The University's pre-eminent obligation is to ensure the academic freedom of all of its members, wherever they work. ...Recent events underscore the importance of the university speaking out in support of the fundamental freedoms of the university, not only in support of individual colleagues, but to create an environment in which all faculty members have confidence they will be protected from improper pressure from any quarter.²

The issue of whether or not the University had lived up to its stated obligation and protected Dr. Olivieri's academic freedom is a significant element of the L1 controversy. The University's position is that it had done so. For instance, the minutes of November 1998 meeting of the University's Governing Council recorded:

A member referred to the President's comments about Dr. Olivieri's current situation in the hospital and noted that a similar situation at the University might raise questions about her academic freedom. The President concurred that ensuring Dr. Olivieri's academic freedom was critical but he reminded members that the information on the test results, which was at the heart of this problem, had been released by Dr. Olivieri in November, 1996.³

The University's twelve-point statement of December 3 said:

Pursuant to the University's commitment to full and free debate, in 1996 the Dean of Medicine *successfully* intervened at the request of Dr. Olivieri to mediate between Dr. Olivieri and Apotex and achieved with the *consent* of both Apotex and Dr. Olivieri the disclosure of Dr. Olivieri's scientific data.⁴ (emphasis added)

A similar statement was made in an article published in the University's newsletter, *The Bulletin*, on December 14, 1998:

The [Naimark] review determined that Dr. Arnold Abeman, Dean of the Faculty of Medicine, had intervened on several occasions on Dr. Olivieri's behalf, including calling on Apotex not to proceed with legal action against her and convening mediation between both parties with the result that she was allowed to disclose her research results.⁵

There is no dispute that Dean Aberman intervened in an effort to protect Dr. Olivieri from improper pressure from Apotex. However, the claims that the Dean had succeeded in 1996 and that no further University action was required are contradicted by documentary evidence. The Dean was copied on legal warnings Apotex issued after his interventions and it is clear from the documentary record that Apotex never consented to Dr. Olivieri's disclosure of her findings on risks of L1. She continued to be subject to improper pressure from Apotex from 1996 onward. There is extensive correspondence 1996 and 1997 involving Dr. Olivieri, her CMPA legal counsel and Apotex's legal counsel which demonstrates that Apotex continued to warn Dr. Olivieri of legal action should disclose her findings. It is clear from this correspondence that her CMPA counsel took these continuing warnings very seriously and that the CMPA devoted substantial resources to contending with these warnings. It is also clear that Apotex infringed Dr. Olivieri's academic freedom through its warnings. (See sections 5H, 5I, 5N(3) and 5T.)

An important unanswered question is why the the full institutional resources of University of Toronto were not deployed to "vigilantly protect" Dr. Olivieri's academic freedom—until January 1999 when it successfully intervened after a further escalation of the controversy, following actions against Dr. Olivieri by HSC.

(2) University involvement in the L1 trials & controversy

The University of Toronto was involved in the trials from the outset. The main sites of the trials were two of the University's fully affiliated teaching hospitals, HSC and The Toronto Hospital (where thalassemia patients received their care after they reached adulthood). The investigators, Dr. Olivieri and Dr. Koren were clinical professors of medicine in the University and as such had the same right to academic freedom as all other professors in the University, as its December 1998 statements confirmed.* Reciprocally, the investigators also had responsibilities to the University for their conduct. We list other aspects of University involvement:

1. The pilot study that became the long-term trial (LA-03) was funded by MRC for four years (1989–1993), and the applicants identified them-

*In a letter published in *The Bulletin* on October 13, 1998, Dr. Cecil Yip, Vice-Dean (Research) of the Faculty of Medicine, said "The Faculty of Medicine's strategic plan, approved by the faculty council No v. 22, 1993, acknowledged that our departments are no longer simply campus-based and as a result we do not distinguish between faculty members based on where they are located or how they are compensated." He added, "The special relationship with the fully affiliated teaching hospitals is far from new."

selves as professors in the University of Toronto. Their applications to MRC were endorsed by Dr. Robert Haslam, Chair of the University's Department of Pediatrics.

2. The quantities of the drug L1 administered to patients in the pilot study were synthesized in the University's Department of Chemistry by a professor of Chemistry, Dr. Robert McClelland.
3. In addition to Dr. Olivieri who was the treating physician of trial participants, monitoring procedures and data analysis were performed by a number of other professors in the University. For instance, liver biopsies were performed by Dr. Laurence Blendis, a professor in the Department of Medicine, and biopsy slides were analysed by Dr. Ross Cameron, a professor in the Department of Pathology.
4. The randomized trial (LA-01) was funded through MRC's "university-industry" program, and the application for the MRC share of the funding required endorsement by an officer of a university. In this instance, Dr. Robert Haslam signed for the "University of Toronto" in his capacity as Chair of the Department of Pediatrics.

After Apotex terminated the trials, issued legal warnings to Dr. Olivieri and withdrew supplies of its drug from the HSC pharmacy, the University accepted that it had responsibilities. It took actions on this basis, including reviews of the conduct of several individuals in matters pertaining to the developing controversy.

1. Dr. Aberman intervened several times in 1996 as Dean of the University's Faculty of Medicine in efforts to protect Dr. Olivieri's academic freedom, as well as to arrange reinstatement of the supply of L1 for those fully informed patients who wished to continue on the drug after the trial terminations, and for whom it was considered sufficiently safe and beneficial.
2. In 1997 the University received a complaint of academic misconduct lodged by Dr. Olivieri in connection with publication of data from the LA-03 trial, and it investigated this complaint (see section 5N(5)).
3. In 1998 the President and Provost "reviewed the conduct of the Faculty of Medicine, its Dean and the Chair of Dr. Olivieri's department" in connection with the L1 controversy, as reported in the minutes of the Governing Council.⁶
4. In 1999 the University intervened and helped to resolve several issues arising from HSC actions against Dr. Olivieri that adversely affected her ability to carry out her research and infringed her academic freedom (see sections 5M(2) and 5N(13)).

5. In 2000 the University received allegations against Dr. Olivieri publicly referred to it by the HSC Board of Trustees and Medical Advisory Committee—allegations pertaining to her conduct that arose from the L1 controversy. The University did not reject this referral and it initiated a preliminary inquiry (see section 5P). (We have no information as to whether the University intends to proceed with a full inquiry.)
6. In 2000, the University disciplined Dr. Koren for “gross misconduct” in breaching his responsibilities to the University in matters related to the L1 controversy (see section 5R).⁷

(3) Responses of administrators to appeals

Dean Aberman responded promptly to an appeal for assistance by Dr. Olivieri and became involved in the L1 dispute in early June 1996, shortly after Apotex terminated the Toronto trials. He had discussions with the parties to the dispute and then held a mediation meeting on June 7, in which certain issues were resolved but others remained unresolved (see section 5G).

Dean Aberman also intervened in regard to the Apotex legal warnings. In a memo to the Naimark Review, he indicated that he considered these actions by Apotex to be inappropriate and that, shortly after the June 7 mediation meeting, he arranged an informal meeting with Apotex President Mr. Jack Kay.⁸ In this meeting Dean Aberman:

advised him [Mr. Kay] that ... Apotexy [sic] should stop threatening legal action against Nancy and should not proceed with legal action. ... Mr. Kay said that he would consider [sic] my request.⁹

Despite this intervention by the Dean, Apotex continued to issue legal warnings to Dr. Olivieri, telling her not to disclose her findings to anyone: patients, the regulators, the scientific community, or other treating physicians. The Dean was copied on warning letters dated August 12, August 22, November 7, and November 27, 1996.¹⁰ In particular, both he and Mr. Kay were copied on the August 12 letter. This should have prompted Dean Aberman to follow up on his informal discussion with Apotex President Kay by another more formal one. However, we have no evidence that he did so, and as to his informal meeting with Mr. Kay in June 1996, he wrote, “I had never met him [Mr. Kay] before (or since).”¹¹ As Dean, he had a responsibility to have taken more effective measures. If he felt unable to do this himself, he could have asked the Provost or the President to assist him. We have no evidence that he took any such steps in 1996, or later.

With the legal warnings continuing through August 1996, Dean Aberman advised HSC Pediatrician-in-Chief Dr. Hugh O’Brodivich that he was dealing with the warnings. Dr. O’Brodivich’s handwritten note dated August 22 (on a copy of the legal warning letter of that date signed by Dr. Spino) said:

Called Arnie A: He was fully aware ... discussions with Spino. Advised he would handle this.¹²

The Dean’s discussions with Dr. Spino were no more effective than his discussion with the Apotex President Mr. Kay had been—the legal warnings continued in the fall of 1996 and in 1997, and none has ever been rescinded. The documentary record is clear: *Apotex never consented* to the disclosure of any of Dr. Olivieri’s scientific data at any time after May 24, 1996 when it issued the first in its series of legal warnings.

Apotex did not initiate a legal action against Dr. Olivieri, but it nevertheless infringed her academic freedom in substantial ways. It is well known that a successful legal strategy is to seek to achieve an objective by issuance of warnings of action, without having to put the matter actually before the courts. Exhausting the resources of an opponent, while expending a comparatively small fraction of one’s own resources and not having to risk a loss in court, is such a strategy. As discussed in section 5H(3), Dr. Olivieri was ultimately able to publish her findings in 1996 because she and prominent supporters convinced the CMPA that publication was important to the public interest. Her CMPA counsel then wrote to Apotex to make clear that she had CMPA backing in the event Apotex proceeded with legal action. We have no evidence of any effective assistance from Dean Aberman or other University officers in this.

Apotex issued more legal warnings to Dr. Olivieri in 1997 to deter her from disclosing findings on L1, and on CMPA legal advice she withdrew conference abstracts already submitted. (See section 5I.) Thus in these instances, CMPA assistance was insufficient to protect her academic freedom. We have no record of any intervention by the University to protect Dr. Olivieri’s academic freedom in 1997, or in 1998, although she continued to be subject to improper pressure from Apotex.

Dr. Olivieri reported to this Inquiry that she concluded in the summer of 1996 that Dean Aberman’s interventions with Apotex were not effective, because the company continued to issue warnings of legal action against her. Dr. Olivieri did not directly seek his assistance again until 1998. Dean Aberman accounted for this break in contact in the following terms.

From June 6, 1996, to August 12, 1998, the day of the Open Meeting, Nancy did not write to me, e-mail to me, or speak to me about the L1 matter. (I was aware, of course, of the continuing controversy because I was copied on many

letters between Nancy and Apotex.) Specifically, after the mediation Nancy NEVER asked me to intervene in any way in the dispute. I thought that was appropriate since most of the letters related to the scientific controversy, first, of the effectiveness, and then, to the possible toxicity of L1.¹³ (emphasis in original)

Many letters from Apotex to Dr. Olivieri disputing her scientific findings, including some that were copied to Dean Aberman, also contained warnings of legal consequences should she communicate her findings to anyone. The fundamental issues were not “scientific,” but instead involved research and clinical ethics, and academic freedom. If a clinical investigator has identified a risk, she has an ethical duty to disclose that risk to research subjects. If a treating physician identifies or learns of a risk, she has an ethical duty to inform patients. As a university professor, an investigator has the right of academic freedom to publish her findings. It is irrelevant to her ethical obligations or her academic rights whether she is eventually proven scientifically correct by independent studies.

Although Dr. Olivieri herself did not approach Dean Aberman for assistance during this two-year period, he was approached on her behalf by a several distinguished scientists and administrators in 1997 (see section 5N(4)). She herself approached two University Vice-Presidents in 1997 and 1998.

In September 1997, Dr. Olivieri met with University Vice-President (Research) Dr. Heather Munroe-Blum to raise several issues. These included the legal warnings by Apotex to Dr. Olivieri, her concern that Dean Aberman had not provided effective assistance to her in the face of these warnings, and the issue of support for her programs. Dr. Munroe-Blum undertook to review “the important policy issue” Dr. Olivieri had raised, and referred her to Provost Sedra “to whom the Dean reports” for her complaint against the Dean.¹⁴ Dr. Olivieri then met with Provost Sedra in October and reviewed two matters with him. These were the findings of the Friedland Committee (which investigated her complaint of academic misconduct against Dr. Sher—see section 5N(5)) to which she objected, and her concern that Dean Aberman had not provided effective assistance to her.¹⁵ A month later, Dr. Paul Gooch, the Vice-Provost wrote to her asking for particulars on the two matters. A few days later, he wrote again advising that she, as a complainant, could not appeal the decision of an investigating committee.¹⁶

On August 1, 1998 Dr. Olivieri again appealed to Dr. Munroe-Blum:

I write to you... with respect to the matter of Apotex and the disclosure of findings arising out of Apotex-supported trials of the iron chelator deferoxamine conducted at the University of Toronto.¹⁷

Dr. Olivieri told Dr. Munroe-Blum she had not pursued her 1997 complaint against the Dean with the Provost because “[she] was concerned that this

might jeopardize [her] employment at The Hospital for Sick Children.” She explained that she took this view because of her treatment by Dr. O’Brodivich who, as Chair of the Department of Pediatrics, reported to the Dean on academic matters. By way of an example, she cited a recent dispute (May 1998) in which Dr. O’Brodivich had “accepted” her “resignation” as Director of the HSC Hemoglobinopathy Program, although she had not resigned. She added, however, that this dispute had been resolved.

The main topic of Dr. Olivieri’s letter to Dr. Munroe-Blum was the L1/Apotex matter. She expressed the view that Dr. Buchwald (Director of the HSC Research Institute) was not taking action to defend medical ethics and scientific integrity from improper influences by Apotex. She mentioned that many physicians and scientists in the Hospital were now expressing support for her concerns, and calling for an independent inquiry. She added that there was growing press interest in the attempts by Apotex to prevent her from communicating with her patients and the scientific community. She noted that this interest would likely be heightened by the impending publication of her article on inefficacy and toxicity of L1 in the *New England Journal of Medicine*, scheduled to appear in the August 13 issue. The letter concluded with a claim that the refusal by Dr. Buchwald and the HSC Administration, and by Dean Aberman to investigate and resolve the L1/Apotex matter “places the protection of patients in clinical trials conducted in this Hospital and University at risk, and is unacceptable from the point of view of scientific integrity,” and a request for advice on how to proceed.¹⁸

Dr. Munroe-Blum responded to Dr. Olivieri’s concerns by writing that Hospital matters should be resolved with the Hospital, and that her complaint alleging inaction by Dean Aberman should be brought to the Provost.¹⁹

Dr. Olivieri then wrote to the Provost, sending him a package of background material. He replied on August 12, 1998, saying he had read the material and had met with Dean Aberman that day. Provost Sedra advised Dr. Olivieri to meet with the Dean who had assured him that he (the Dean) “is prepared to” assist her “in resolving the matters in dispute.”²⁰

Dr. Olivieri approached Dean Aberman on August 12, 1998 to ask for assistance, while they both were attending an “Open Meeting” at the Hospital. The meeting was called by Mr. Strofolino and Dr. Buchwald, in response to a petition to Dr. Buchwald signed by many staff asking for an independent investigation of the issues raised by the Apotex affair (see section 5L(3)). It was held the day before Dr. Olivieri’s article on the toxicity and inefficacy of L1 was to be published in the *New England Journal of Medicine*, an upcoming event known to many. Dean Aberman and Dr. Olivieri met again and exchanged correspondence. On August 18, 1998 she requested a full and impartial inquiry into the L1 dispute, and

support for her clinical and research programs.²¹ Dean Aberman responded by letter on August 20, 1998 saying the principal matters in dispute involved the Hospital so that,

In these circumstances, in my judgment, it would be inappropriate for me as Dean, in the absence of any allegation of a breach of University policy, to launch an inquiry at this time.... However, if any specific allegation of a breach of U of T policy is made ... I will, as I have in the past in this matter, immediately institute appropriate proceedings.”²²

The University has policies on academic freedom and on the ethical conduct of research. Dr. Olivieri’s academic freedom had been infringed repeatedly by Apotex in efforts to prevent her from disclosing her findings. Apotex had also attempted to impede Dr. Olivieri from complying with the ethical obligations of clinical professors. Dr. Olivieri had stated at the outset of the dispute, in her May 25, 1996 letter to her Department Chair, Dr. Haslam, copied to Dean Aberman, that the company was “attempting to suppress data” on the risk she identified, and that its legal warnings had “ethical implications for the safety of patients.”²³ Dean Aberman himself recognized in 1996 that Apotex was acting inappropriately when he intervened with Mr. Kay and Dr. Spino in the summer of that year. It is therefore hard to understand the Dean’s apparent contention that there was no specific allegation of a breach of University policy in this matter.

(4) Efforts by scientists to assist Dr. Olivieri

As noted in section 5L, several of Dr. Olivieri’s HSC colleagues, notably Dr. John Dick and Dr. Peter Durie, had approached HSC administrators and Dean Aberman in 1997 to seek a resolution of the L1 dispute. Scientists from outside the Hospital and the University also became involved in such efforts.

In July 1997, Dr. Michael Baker (Physician-in-Chief of The Toronto Hospital) raised with Sir David Weatherall (Regius Professor of Medicine, Oxford) his concerns about the treatment of Dr. Olivieri by Apotex and about the perceived lack of support for her by the Hospital for Sick Children and the University. Sir David then wrote to Dean Aberman, reviewing these concerns, which he shared. He outlined Dr. Olivieri’s accomplishments as a clinician and scientist, and explained the international importance of her clinical and scientific programs.²⁴ Sir David expressed the hope that the Dean could be of some assistance to her. Dean Aberman responded saying that, “It is my view that Nancy has been given appropriate support in this matter by both the University of Toronto and the Hospital for Sick Children.”²⁵

Dr. David Nathan (President of the Dana Farber Cancer Institute, Harvard) contacted Dean Aberman that summer with similar concerns and received a

similar response.²⁶ The Dean then met with HSC Executive members, Drs. Goldbloom, O’Brodivich and Buchwald, on September 2 to discuss the concerns raised by Sir David and Dr. Nathan. “After discussing the matter, [they] agreed that no further action is necessary at this time.”²⁷

In July 1997, Dr. Robert Phillips (Executive Director of the National Cancer Institute of Canada) also interceded with Dean Aberman. Dr. Phillips reported this discussion to Dr. Olivieri:

His [Dr. Aberman’s] position is that he has supported you from the beginning... He feels that because you signed the original agreement with Apotex, they have every right to enforce the agreement...²⁸

Subsequently, in September 1997, Dr. Phillips sent a lengthy letter to Dean Aberman and Drs. O’Brodivich and Buchwald, expressing again his concern that they had not assisted Dr. Olivieri “in her battle with Apotex” and in other matters.²⁹ They replied to Dr. Phillips, telling him he was misinformed. The Hospital administrators also said that they were “personally offended” and noted he wrote to them on letterhead of the National Cancer Institute of Canada and signed as Executive Director. They asked if his letter therefore represented the position of the NCIC and they also wrote to his employer raising the same question.³⁰

(5) The Friedland Investigating Committee

Several major aspects of the L1 controversy involve the publication of abstracts for scientific conferences. Abstracts are usually considered less important than articles in scientific journals. However, in this matter, abstracts were centrally important for several reasons:

- The abstracts Dr. Olivieri wished to publish in 1996 and 1997 reported findings of unexpected risk of a drug (L1) that was being used in several countries, and physicians and thalassemia patients should know of these risks.³¹
- Apotex attempted through legal warnings to deter Dr. Olivieri from publishing these abstracts, thereby violating her academic freedom.³²
- While attempting to prevent Dr. Olivieri from disclosing risks, Apotex published its own abstracts with Dr. Koren reporting that L1 was effective and safe, and used such publications in a Priority Review Submission to Health Canada.³³

A significant venue for presentation of findings of unexpected risks of L1 was the 6th International Conference on Thalassemia and the Hemoglobinopathies held in Malta in April 1997, and Apotex attempted to prevent Dr. Olivieri from presenting an abstract there. In the face of Apotex’s legal warnings and on the advice of her CMPA legal counsel, she withdrew her already

submitted abstract. When she later obtained (through counsel) copies of two abstracts based on data from the LA-01 and LA-03 trials to be presented by Apotex at that conference, she re-submitted and presented her abstract, with CMPA legal support. (See section 5I.)

The first author of the two abstracts giving Apotex's interpretation of the data was a company employee, Dr. Fernando Tricta. He had been hired around the time the Toronto trials were terminated by the company and had not been involved in these trials. Dr. Koren and his Apotex-funded research fellows were co-authors on both abstracts, and Dr. Koren was listed as senior author on both.³⁴ Neither abstract acknowledged Dr. Olivieri's contributions to generating the data reported, and neither referred to her abstracts presented at ASH in December 1996 on data from the same trials. Neither disclosed the Apotex funding support received by the authors (except for giving Dr. Tricta's Apotex address).

Following the Malta conference, Dr. Olivieri lodged a complaint of academic misconduct under Faculty of Medicine procedures against Dr. Graham Sher, a co-author of the abstract based on data from the long-term (LA-03) trial.* It concluded that L1 was effective (and hence safe) in the long term in "the majority" of patients in that trial.³⁵ We have not been given a clear and compelling account as to why similar complaints were not lodged against Dr. Koren or other co-authors at that time. This complaint and the investigation of it are factors in what was then a still-growing controversy, and a discussion of them sheds light on several aspects of the wider dispute.

Dr. Sher came to Toronto in 1993 to study as a research fellow with Dr. Olivieri. By his own account, she greatly assisted him in advancing his career.³⁶ He wrote letters in 1994 and 1995 expressing appreciation not only for her scientific and clinical mentoring, but also for making efforts to ensure that both he and his family felt personally welcome in their new city. For instance, in 1995 Dr. Sher wrote:

Dr. Olivieri was an inspiration to me, and an enormous support in helping me launch my career.... [she provided] unwavering support in my research projects and... tireless encouragement to excel in research I recall many hundred hours of highly informative scientific discussion between us. Through all of this, Dr. Olivieri remained personable in the extreme, and treated me as much a colleague as a fellow, and also as a friend and confidant. She encouraged, indeed supported, me to attend as many meetings as possible, and introduced me to her colleagues worldwide, which has greatly benefited my own career. She was always willing to have me present our joint data.... In

*The Investigating Committee's report on this complaint was discussed in the Naimark report (p. 67) and the full report is contained in the Naimark Report's archive in the HSC library. The report was also discussed in an article in the *National Post* on December 23, 1999.

addition, Dr. Olivieri provided outstanding direction and support as a clinical supervisor...³⁷

Dr. Sher was subsequently appointed as an assistant professor of medicine in the University and as a staff physician in The Toronto Hospital (TTH). He was appointed Director of the Hemoglobinopathy Program in TTH in July 1995.³⁸ Early in 1996 he signed a contract for “a one-year consultancy for Apotex Inc. for which [he] was paid the sum of \$15,000.”³⁹

On May 24, 1996 Apotex terminated the Toronto L1 trials (LA-01 and LA-03). Dr. Olivieri reported to this inquiry that subsequently in 1996 she and Dr. Sher had a disagreement concerning the efficacy of L1, and that she discussed this with senior hematologists in TTH.⁴⁰ The University Investigating Committee that considered Dr. Olivieri’s complaint regarding the 1997 Malta abstract reported that:

In the summer of 1996... the relationship [between Sher and Olivieri] deteriorated and he was eventually advised by more senior people in the hospital [TTH] to move to the blood transfusion service in the hospital, which he did at the beginning of 1997. This was not initially Dr. Sher’s wish: he had a strong interest in the fields he was exploring and in which he was building a good professional reputation.”⁴¹

In January 1997, The Toronto Hospital appointed Dr. Olivieri to replace Dr. Sher as Director of its Hemoglobinopathy Program.

Of the six co-authors of the LA-03 abstract, Dr. Sher was the only hematologist who had also treated patients in the trial as a hospital staff physician.⁴² The data were collected during the early, MRC-funded phase, as well as through the later, post-1993, Apotex-supported phase. The abstract included tables of data on iron loading of patients for each year from 1989 to 1996. It presented a conclusion on the efficacy of the drug L1 incompatible with the conclusion of the abstract Dr. Olivieri had presented at the American Society of Hematology (ASH) meeting in December 1996 for the same trial (see section 5H). The abstract by Dr. Sher, Dr. Koren, Dr. Tricta and others made no mention of the risk of loss of sustained efficacy Dr. Olivieri identified in 1996 and published in her December 1996 ASH abstracts. It also made no mention of the risk of progression of liver fibrosis she had identified in early February 1997, of which she had then informed Apotex and Dr. Koren. Both these risks were identified in data on the same LA-03 group of patients.⁴³

Shortly after the April conference, Dr. Olivieri wrote to Dr. Sher demanding an explanation and an apology for his part in publishing data generated by Dr. Brittenham and herself, without their “review, consent or participation.”⁴⁴ She also stated (incorrectly) that “the presence of your name on this abstract has been agreed upon to represent research misconduct on your part.” This does not state by whom, but it does incorrectly imply there had been some

kind of formal evaluation. She advised Dr. Sher that she had discussed her concerns with Drs. Armand Keating and Michael Baker, to whom Dr. Sher reported at TTH, and with Dr. Cecil Yip, Vice-Dean (Research) in the Faculty of Medicine. She also told him that she would proceed with a formal complaint of academic misconduct under the Faculty's policy on such matters,⁴⁵ if he did not provide a satisfactory account. In her letters she alleged plagiarism and fraud* under the Faculty's policy on such matters.⁴⁶

Dr. Sher addressed a lengthy reply to Dr. Keating on June 2. In this he stated:

I confirmed prior to consenting to my name being on the abstract that (i) Apotex had ownership of, and hence the right to publish, the data and (ii) that Dr. Koren, as coinvestigator, would be senior author on the abstract.⁴⁷

However, the abstract by Tricta, Sher *et al.* included data generated by Dr. Olivieri during the four years 1989 and 1993, before Apotex's involvement in this trial began in the spring of 1993. The 1995 contract for the LA-03 did not say that Apotex had ownership of data—it stated only that Apotex would be provided with “the information they require for Regulatory purposes.”⁴⁸ Furthermore, although Dr. Koren was a co-investigator in the trials, his direct scientific role was mainly in pharmacokinetics. The tables in the abstract on measures of iron loading used data generated by Dr. Olivieri and (in the case of hepatic iron concentration [HIC] after 1992) Dr. Brittenham. There was no contract between Apotex and Dr. Brittenham for either the LA-01 or LA-03 trial.

Dr. Sher's responses to Dr. Olivieri's allegations in his letter to Dr. Keating were unsatisfactory to Dr. Olivieri, and she proceeded with a formal complaint. Under the procedure of the Faculty of Medicine⁴⁹, Dr. Eliot Phillipson, Chair of the Department of Medicine, undertook a preliminary review. He concluded that her allegations were “not ‘frivolous, vexatious, or clearly mistaken,’ and that the process should therefore proceed to the stage of investigation.”⁵⁰ A three-person “Investigating Committee,” chaired by Professor Martin Friedland of the Faculty of Law, was then convened.

The Friedland Investigating Committee reported in September 1997. It found that:

... [I]n the circumstances of this case, ... within in the meaning of those terms in the 1996 Framework for Ethical Conduct of Research... **no fraud,**

*The University's *Framework for Ethical Conduct of Research and Guidelines to Address Research Misconduct* includes under the heading “Misleading publication (fraud),” the following: “giving or receiving honorary authorship... denying legitimate authorship... publication of data for a second time without reference to the first.”

plagiarism, misconduct or serious scientific error was committed by Dr. Sher.⁵¹ (emphasis in original)

However, the Investigating Committee did criticize the authors of the abstract:

The authors of the Malta abstract can certainly be faulted for a lapse in judgment in not giving Dr. Olivieri an opportunity to comment ... [and] The Malta abstract should have included some acknowledgement of Dr. Olivieri's contribution to the development of the data.⁵²

The Investigating Committee also criticized Dr. Olivieri for bringing the complaint:

All members of this committee have enormous sympathy with the position now faced by Dr. Sher. In our view, Dr. Olivieri used poor judgment in bringing these very serious charges against a junior colleague in these circumstances.⁵³

The Investigating Committee noted that the abstract had been drafted by Apotex: "It was prepared by them and submitted to Dr. Koren...."⁵⁴ However, the only acknowledgement of Apotex support in this abstract (and in the other abstract for the Malta conference by Dr. Tricta *et al.*) was an indication that Dr. Tricta was an Apotex employee. This was despite the facts that Dr. Sher had a consulting contract with Apotex, Apotex funds for the Toronto trials were deposited in Dr. Koren's research grant accounts, additional Apotex funds were provided to his accounts after the trial terminations, and his research fellows received salary support from these funds during and after the trials. The Investigating Committee suggested that it would have been preferable for the authors to have provided more details on their financial and other connections with Apotex. It proposed that the Faculty of Medicine consider strengthening its disclosure requirements in accordance with internationally accepted guidelines for publication in medical journals.⁵⁵

Some of the Friedland Investigating Committee's findings are difficult to understand. First, in the University's *Framework* document, "publication of data for a second time without reference to the first," is included in the "list of acts generally considered to be instances of serious misconduct." The data had already been published by Dr. Olivieri and at least some authors of the April 1997 Malta abstract knew this, but made no reference to the previous finding in their abstract. The Investigating Committee acknowledged this fact* yet apparently did not find it important, possibly because "almost everyone who was working in the specific field would have known about the controversy."⁵⁶ This statement is of concern because: (i) no basis is provided for the pre-

*Dr. Koren and Apotex were sent copies of Dr. Olivieri's December 1996 ASH abstract before she submitted them, and she offered co-authorship to Dr. Koren but he declined. The Investigating Committee reported (page 5) that, "almost everyone working in the field would have known about the controversy," and that in addition to her ASH abstract, "she had published a major article in the important journal, *Blood*, which had come out in February, 1997... in which she presented her views on the danger of using deferiprone."

sumption that almost everyone in the field would have known; (ii) it does not absolve the authors of a responsibility; and (iii) Apotex was trying through legal warnings to suppress information it disagreed with—an important instance being its warnings against Dr. Olivieri’s own presentation at the same April 1997 meeting in Malta. It was only when she finally obtained a copy of the abstracts by Dr. Tricta *et al.* shortly before the meeting, that she obtained legal backing from the CMPA to defy the legal warnings and re-submit her abstract. Had the CMPA not provided support, it is possible that some scientists who attended the Malta meeting would not have learned of the risks of L1 identified by Dr. Olivieri, or of the controversy.

Second, the Investigating Committee appears to have simply accepted that Apotex owned all of the data. This was not the case, as noted above. It is a serious omission that the claim that Apotex owned the data was not addressed by the Investigating Committee, as it directly relates to the complaint it was asked to investigate.

Third, the Investigating Committee concluded that no “serious scientific error” was committed even though it acknowledged it was not equipped to evaluate this question:

This committee is, of course, not qualified to decide that [scientific] dispute... For this reason, we did not hear additional witnesses whose evidence would relate primarily to the scientific merits of the controversy.⁵⁷

Thus it appears that the Investigating Committee reached the conclusion that Dr. Sher (and by implication his co-authors) committed no “serious scientific error” without the benefit of an appropriate investigation.

The Investigating Committee also reported uncritically Dr. Koren’s testimony that he agreed with both of two incompatible views regarding the efficacy of L1. The Committee’s report described Dr. Koren’s position as follows:

Dr. Koren agreed with Apotex’s interpretation, recommended a number of changes, and allowed his name to be used on the abstract [delivered in Malta in April 1997]. In fact, *he also agreed with Dr. Olivieri’s earlier abstract* delivered in Orlando [in December 1996], but did not allow his name to be used because he felt that there were less dramatic ways of resolving the issues. In his view, the abstracts looked at the data from different perspectives.⁵⁸ (emphasis added)

Whatever the perspectives were, the two conclusions were incompatible. It would have been very surprising to the scientific community if Dr. Koren had allowed his name to be used on two abstracts which had contrary conclusions. This was a central matter: Apotex opposed Dr. Olivieri’s findings and had been issuing legal warnings to prevent her from communicating them to patients, to the regulators and to the scientific community. In particular, it issued legal warnings specifically to deter her

from presenting her abstract at the December 1996 ASH meeting. In the summer of 1996, Dr. Koren had asserted to Dr. Olivieri, in the presence of their joint CMPA legal counsel, that he agreed with her findings as expressed in the ASH abstract. When consulted on that abstract, he proposed only minor wording changes, but later declined to be included as a co-author allegedly because of the Apotex legal warnings.⁵⁹ The point of the April 1997 abstract, on which Dr. Koren was a co-author, was specifically to oppose Dr. Olivieri's findings. The lack of discussion by the Investigating Committee on this issue is hard to understand, because Dr. Koren allowed his name to be used as *senior* author on abstracts presented by an Apotex employee and that clearly served the company's interest.

Section 5.2 of the Framework for Ethical Conduct of Research states:

When an investigation determines that no fraud, misconduct or serious scientific error was committed, the Dean shall ensure that a letter confirming full exoneration is sent to the accused, with a copy to the complainant and to all other persons with knowledge of the accusation.⁶⁰

In accordance with this policy, Dean Aberman sent a letter to Dr. Sher with copies to eleven other individuals, stating that the Investigating Committee had “concluded that ‘no fraud, plagiarism, misconduct or serious scientific error was committed by Dr. Sher,’” and confirming “full exoneration.”⁶¹ Dean Aberman included a second quotation from the report, “In addition all members of the Committee had ‘enormous sympathy with the position’ that you faced.”⁶²

As noted above, the Investigating Committee recommended that the Faculty of Medicine consider strengthening its requirements for disclosure of all financial support for research. It appears that effective steps to implement this recommendation have not been taken by the Faculty. In 1999 the website of the Faculty of Medicine listed a research grant for Dr. Koren of \$250,000, given in 1995–96 for use in 1996–97, but did not specify the source or purpose for this large sum. It was later ascertained that the source was Apotex. Also in 1999, Dr. Koren published an article on L1 in a scientific journal, with two of his research fellows as co-authors.⁶³ Dr. Koren's research was funded by Apotex and the two co-authors, Dr. Orna Diav-Citrin and Dr. Gordana Atanackovic, received salary support from Apotex funds provided to Dr. Koren, but nowhere in the article is Apotex noted as a source of financial support for the work. (See sections 5G and 5R.)

Questions arising from Dr. Koren's conduct in regard to the Malta abstracts, as well as dissatisfaction in some quarters with the report of the Investigating Committee, resulted in the issues being pursued (see section 5L).

(6) Statements about the University's Publication Policy

The University made public statements that had the effect of suggesting that Dr. Olivieri was the author of her own misfortune by signing “the contract.” Point 3 of the University’s twelve-point statement of December 3, 1998 said that:

The contract entered into by Dr. Olivieri with Apotex violated University policy and would not have been administered by the University. We agree with Dr. Olivieri that she made a mistake in signing the contract which included offensive publication restrictions.... The University... is committed to full and free debate... and therefore prohibits contracts... which improperly restrict the timely release of research results.

A similar statement was made by President Prichard, as recorded in minutes of the Governing Council meeting of February 1999:

The President noted that the signing of the contract between Dr. Olivieri and a pharmaceutical company that lay behind this whole matter would have been prohibited by the University. No contract entered into by the University could contain a clause prohibiting publication of research results.⁶⁴

These statements cause concern because they are not correct and do not in fact represent University policy. The University’s Publication Policy, in force since 1975, permitted a publication ban by a sponsor of contract research in cases where “the sponsor has industrial or commercial rights to protect” of “12 months” and, in exceptional circumstances, “24 months” after the conclusion of a study.⁶⁵ Therefore, it is hard to understand that the President would suggest that its policy would not permit publication delays. Vice-President Munroe-Blum had earlier informed the Academic Board that, “Twelve months was the maximum delay allowed.”⁶⁶ Dean Aberman, replying to Dr. Paul Ranalli in February 1997, “at President Prichard’s request,” said, “the University of Toronto accepts a *reasonable* delay in publication when requested by the sponsoring company.”⁶⁷ (emphasis in original)

The statements above referred to “the contract” signed by Dr. Olivieri. However, there were three contracts, related to three separate L1 trials: The Toronto-based trials LA-03 and LA-01, and the international trial LA-02. The trials and contracts are described in sections 5A and 5B. The only contracts relevant to the data Dr. Olivieri wished to disclose were the LA-03 and LA-01 contracts.

The dispute over Dr. Olivieri’s findings arose from data of patients in the long-term (LA-03) study, which had no publication ban, although surprisingly, this fact seems to have been overlooked. The contract for the randomized trial (LA-01) had a one-year post-termination publication ban, so it too was in accordance with the University’s Publication Policy. All but one of the legal

warnings of which we are aware, were issued within twelve months of the termination of the trials, the delay period *allowed* by University policy and the delay period specified in the LA-01 contract. However, the findings which the Hospital's Research Ethics Board had directed Dr. Olivieri to disclose were not covered by any publication ban, since they were derived solely from LA-03 data and the contract for the LA-03 trial had *no* confidentiality clause.

There are indications that the University administration may at times have been referring to the LA-02 consulting contract for work in Italy, with its three-year ban, in its statements about "the contract."⁶⁸ This view is reflected in the report by Professor Bernard Dickens commissioned by the President to provide advice on harmonization of research policies between the University and the teaching hospitals. Professor Dickens contrasted the publication restriction in the LA-02 consulting contract with that permitted by University policy, and remarked that "investigators who are physicians, treating subjects who are also patients for whose well-being they are clinically responsible, cannot bind themselves to sponsors of studies in ways that compromise discharge of their legal and ethical duties to their patients."⁶⁹ However, Dr. Olivieri was not the treating physician of any patient in the international (LA-02) trial and, under FDA regulations, she could not be an "investigator" for this trial. She was retained as a consultant to design the trial, and engage and train site investigators.

Even if an argument could be made that the LA-02 contract was relevant to data from the LA-03 trial when the LA-02 contract was signed in June 1995, by October 1995 when the LA-03 contract was signed any such argument was nullified. The LA-03 contract expressly "supplanted" any earlier agreement concerning data for that trial and it contained no confidentiality clause.

The University policy itself, in allowing a twelve-month publication ban, posed the problem that if a risk discovered in a clinical study involved acute toxicity, then even a few weeks could be too long.

The question arises as to the University's purpose in stating it did not allow contracts with publication restrictions, when in fact its *Publication Policy* did allow restrictions. We do not know the answer. However, the effect was to lend weight to the view that Dr. Olivieri was the author of her own misfortune. These statements also deflected attention from a serious weakness in the current University policy as it applied to clinical research. Professor Dickens' observation (quoted above) pointed to a serious shortcoming in the existing University policy that needed to be addressed.

In March 2001, the University announced that its publication policy was being changed, so as to prohibit confidentiality clauses that could be used by industrial sponsors in efforts to suppress information on risks to health

identified in clinical trials.⁷⁰ This important policy advance provides confirmation by the University itself that: (i) its previous policy did allow such clauses in contracts, contrary to statements made by senior officers in 1998–1999; (ii) the previous policy was inappropriate for clinical trials. The *Toronto Star* reported on March 27, 2001 that:

U of T's dean of medicine Dr. David Naylor said he believed if the new research policies had been widely implemented [a decade earlier] the whole Olivieri-Apotex conflict would likely have been avoided.⁷¹

(7) The Joint Centre for Bioethics

The Joint Centre for Bioethics is a partnership between the University and a number of health care institutions. Staff bioethicists of HSC and other hospitals are members of the Joint Centre. Its website states: “Our mission is to provide leadership in bioethics research, education, and clinical activities.” The efforts by Apotex to deter Dr. Olivieri from informing patients about risks she had identified, and the lack of effective support for her by HSC and the University, gave rise to one of the most significant and highly publicized bioethical disputes in Canada in many years. Yet the Joint Centre for Bioethics appears not to have provided leadership in this matter.

Dr. Peter Singer, Director of the Joint Centre, declined to meet with this committee of inquiry and, instead, informed us in writing that:

The involvement of the Joint Centre was through the work of two of its members—Dr. Christine Harrison and Professor Mary Rowell—who are the Bioethicists at the Hospital for Sick Children. I understand that they have already met with you in this matter.⁷²

Professor Rowell's involvement is outlined in section 5.L(2). Dr. Harrison, who is Director of the Hospital's Bioethics Department, explained her lack of involvement in the matter. She agreed with Professor Rowell's view that the central issue was one of ethics because a private company was attempting to deter a clinical investigator from disclosing risks of its drug, and that scientific disagreement was not the central issue.

The Joint Centre, as a centre, appears not to have been engaged or to have spoken publicly on the controversy. Its silence is hard to understand.

(8) The University & the Naimark Review

After Dr. Olivieri's paper on the chronic toxicity and inefficacy of L1 appeared in the *New England Journal of Medicine* in mid-August 1998, there was national and international publicity regarding the Apotex legal warnings not to disclose risks and the apparent failure by the Hospital and the University to

provide support against this. Pressures developed through the following weeks for an independent inquiry. Although Dr. Olivieri's academic freedom had been repeatedly infringed by Apotex's actions the University took the position that responsibility lay primarily with the Hospital. It outlined its position in a December 1998 statement:

The circumstances at the Hospital for Sick Children involving Dr. Olivieri and Apotex required a prompt review and full public disclosure of all relevant facts. The University intervened to encourage the Hospital to undertake a review and supported the review when it was announced. This is the Hospital's review, not the University's.⁷³

The Naimark Report characterized the University's position in similar terms:

For its part, the University took the view that the L1 clinical trials controversy was primarily a Hospital matter, since the University was not involved in the processes involved in the establishment, conduct or financing of the trials, and since no breach of University policy had been alleged that had not already been dealt with.⁷⁴

The Naimark Report appears to have accepted the University's position, and did not address the University's responsibility in regard to academic freedom. However, the University was involved in "the processes involved in the establishment, conduct or financing of the trials." (See section 5N(2).) Furthermore, it was clear from documents available to the Naimark Review that Dr. Olivieri's academic freedom had been repeatedly violated by Apotex's legal warnings, and the Report noted that the warnings had continued.⁷⁵

In October 1998, while the Naimark Review was in progress, the matter of the University's involvement was discussed by the Academic Board. The minutes for October 8, 1998 recorded that, "The University had strongly urged the Hospital to carry out a review and the President was pleased that the Hospital had acted.... he and his colleagues had met with Dr. Naimark and had promised their full cooperation." When questioned by a member of the Academic Board about the appropriateness of "a single-person review," "The President indicated that it was the Hospital which had decided the process and he suggested the member provide his advice directly to the Hospital." Ms. Holly Baines, a graduate student representative at the Board meeting, is recorded in the minutes as having expressed concerns that it was her understanding that the Naimark Review had been established without consulting Dr. Olivieri as to the choice of the reviewer or the terms of reference, and that Dr. Olivieri's suggestion of a second person to join Dr. Naimark had not been agreed to by the Hospital. Ms. Baines expressed the concern "that the President's suggestion about writing a letter [to the Hospital] would not do any good."⁷⁶ The minutes recorded the President as having responded by saying he believed policies were in place to prevent "another occurrence of this type."

Regardless of which institution had primary responsibility to establish an inquiry, the University might have endeavoured to use its moral authority and its affiliation agreement in an effort to influence the Hospital to agree to establish a truly independent inquiry from the outset—one that would have had greater prospects of attracting cooperation of all parties to the dispute than was the case with the Naimark Review. Alternatively, it could have proposed to sponsor a joint inquiry. We have seen no evidence that it did either. After the Naimark Review was underway and was itself the subject of controversy, the University made efforts to have the process improved. However, the late interventions by several parties were only partially successful and, in the end, the Naimark Report did not resolve the controversy. (See section 5O.)

(9) An important undertaking

In paragraph 9 of its twelve-point statement of December 3, 1998, the University gave an undertaking to protect the legitimate interests of faculty members employed by HSC following receipt of the Naimark report:

The University has advised the Hospital, and the Hospital has agreed, that after receipt of the Naimark review, the Hospital must review thoroughly with the University any contemplated adverse action against any faculty member of the University of Toronto working at the Hospital prior to any such action taking place. We have also made clear, and will continue to make clear, that we will protect the full rights, privileges and freedoms of our faculty colleagues.⁷⁷

The importance the University placed on this undertaking was stressed by President Prichard to the Governing Council on December 17, 1998. The minutes record that the twelve-point statement was tabled at the meeting, that “The President specifically drew attention to [this] paragraph in the document,” and that the President said that this paragraph specifically applied to Dr. Olivieri.⁷⁸

After receipt of the Naimark Report, the Hospital took serious adverse actions against Dr. Olivieri. First, on the same day the report was released to the public, the Board of Trustees directed the HSC’s Medical Advisory Committee (MAC), the body that advises the Board on disciplinary and medical matters to consider a “failure” by Dr. Olivieri, a matter arising from an (erroneous) finding in the Naimark report. This action was announced publicly. We do not know whether this action was reviewed with the University prior to its being taken. Second, on December 16, 1998 the Combined Chiefs of the HSC Department of Pediatrics, on a matter brought to their attention by the Chair, Dr. O’Brodivich, passed a motion recommending that Dr. Olivieri be removed from the position of Director of the Hemoglobinopathy Program. The Hospital acted on this motion on January 6, 1999. In this instance, the Hospital did review with the University its contemplated action, on January 4. The University then advised the Hospital that the summary removal procedure it intended to use was quite inappropriate. The Hospital nevertheless proceeded as it had intended. Third, also on January 6, 1999, the Hospital issued “gag orders” to Dr. Olivieri, and her supporters, Drs. Chan, Durie and Gallie, in direct violation of their academic freedom. This action was taken without prior consultation with the University (see sections 5M(2) and 5N(13)). Fourth, on April 27, 2000, the Hospital publicly referred enumerated lists of allegations against Dr. Olivieri by the MAC to the University and to the College of Physicians and Surgeons (see section 5P). We do not know whether the University was consulted on this fourth adverse action.

It was clear to the University, and to the UTFA and the CAUT (both of whom had begun providing assistance to Dr. Olivieri in November 1998 —see section 5S), that the Hospital had acted with complete disregard for due process in the removal of Dr. Olivieri from her position as Director. This should have suggested to the University, UTFA and CAUT that there was some probability that due process would not be provided to Dr. Olivieri in the MAC proceedings. They should have made inquiries of the Hospital on the MAC procedures, and the University, at least, had a right to expect an answer. We have no information as to whether such inquiries were made by the University, or if so, what the Hospital's response was. We do know that UTFA and CAUT failed to make such inquiries and we have not been provided with a compelling reason for this. (The MAC proceedings and its denial of due process to Dr. Olivieri are discussed in section 5P and 5Q.)

(10) Harmonization of policies & procedures

The Naimark Report outlined the need for improvements in a variety of policies and procedures. Both the Hospital and the University then undertook substantial initiatives in this regard. In its twelve-point statement, issued several days before the Naimark Report was publicly released, the University announced that:

[T]he University intends to review its relationships with all of its affiliated teaching hospitals to ensure that the circumstances of faculty members working in these hospitals are fully consistent with the University's policies and the protection of our colleagues rights, privileges and freedoms as members of the University.⁷⁹

The Dickens Report. Early in 1999, President Prichard initiated a review of a group of policies pertaining to research. He established a process to facilitate "Harmonization of Research Policies and Procedures Between the University and our Affiliated Teaching Hospitals" with Professor Bernard Dickens of the Faculty of Law as "special senior advisor." Professor Dickens submitted a report in April 1999.⁸⁰ The terms of reference the President had provided to him included a nine-point list of "relevant University policies that we wish to have Professor Dickens consider."⁸¹ The list was substantial, but there were significant omissions from the President's list of topics. For instance, the University's policy on academic freedom was nowhere mentioned, despite the prominence given to academic freedom by the President in public statements made in December 1998.⁸² This omission is further surprising because the 1998 *Tri-Council Policy Statement on Research Involving Humans* highlights academic freedom among the principles guiding ethical conduct of research in Canada.

Subsequently, the Faculty Association objected to this and other omissions from the terms of reference.⁸³ In his meeting with the present committee of inquiry in November 1999, Professor Dickens said that he agreed that academic freedom was important. He added that he intended to take into account the concerns of UTFA in submitting a final report on harmonization of policies.⁸⁴

Announcement of a change to the University's publication policy. Representatives of the Faculty Association and the new Dean of Medicine, Dr. David Naylor (who succeeded Dr. Aberman as Dean in July 1999), had a series of discussions on needed improvements to policy, as well as harmonization of policies between the University and its affiliated teaching hospitals. Among the topics was the need for a change in the publication policy, so as to prohibit confidentiality clauses in research contracts under which industrial sponsors could prevent clinical researchers from disclosing risks. Dean Naylor took up these matters with the hospitals, and established committees to review various matters pertaining to research policy, including the ethical conduct of research, publication and conflict of interest.

On March 26, 2001, Dean Naylor announced that the University, the Faculty of Medicine and the affiliated teaching hospitals had “embarked on an ongoing process designed to harmonize and upgrade the research policy environment,” and that the hospitals had moved important matters “partly or fully through their governance structures,”⁸⁵ among them a “Template Schedule” for the affiliation agreements between the University and each of the teaching hospitals. The section of the template on “Publication” included the following provisions:

University and hospitals agree that they will not enter into agreements that allow research sponsors to suppress or censor research results.

University and hospitals agree that, in agreements with sponsors, delays in publication of research results will normally be limited to a maximum of six months and in no case will exceed twelve months.

University and hospitals agree that agreements with sponsors shall have provisions to permit the public disclosure of research results if required to protect the health of patients.

University and hospitals agree that all contracts with sponsors will contain provision for the effective resolution of disagreements between the sponsor and the researchers.⁸⁶

These new policy provisions could represent a very important advance, provided there are procedures in place to promote and enforce them. It would also be essential to ensure that any mechanism for “resolution of disagreements between the sponsor and the researchers” could not be used to unduly delay “public disclosure of research results if required to protect the health of patients.”

These changes in publication policy make it clear that the previous policy was seriously deficient as it applied to clinical research.

The need for effective grievance procedures. Another policy area addressed in the Naimark Report was the absence of effective grievance procedures for scientific and medical staff in the Hospital for Sick Children. We see, more generally, a need for affiliation agreements between the University and its teaching hospitals to include provisions dealing with a variety of terms and conditions of employment for hospital staff who hold academic appointments in the University. Such matters were emphasized in a memo to us from Dr. John Evans, a former president of the University of Toronto and a member of the Board of the HSC Foundation, as discussed in section 3.C.

A further difficulty at present for professors working at teaching hospitals in pursuing grievances through the University over matters that relate both to their university work and hospital work, such as academic freedom, is that the hospital may not cooperate with the university process. For example, in the present case, when Dr. Olivieri *et al.* requested documents from HSC for their University grievances, officers of the Hospital for Sick Children filed an application in Ontario Superior Court in an effort to block summonses for documents issued by the University Grievance Review Panel.⁸⁷

(11) Dr. Spino

The Apotex employee who negotiated all three L1 contracts for the company and who was prominent in its infringements of Dr. Olivieri's academic freedom, Dr. Spino, holds the same status of professor in the University as Dr. Olivieri and Dr. Koren. We agree with the University that Dr. Olivieri was "entitled to... vigilant protection of her academic freedom," because of her position as a professor. All those who are professors have an obligation to uphold and protect that freedom for their colleagues and themselves. We are in agreement with the University when Dr. Koren's violation of the academic freedom of Drs. Chan, Durie, Gallie and Olivieri was cited as a factor in the disciplinary action imposed on him.⁸⁸ An unanswered question is: Why has the University not also held Dr. Spino accountable for infringing Dr. Olivieri's academic freedom? Although he became a fulltime employee of Apotex in 1992, his status as a professor in the Faculty of Pharmacy has continued since that time, his membership in the Graduate faculty of the Department of Pharmaceutical Sciences being renewed in 1998 for a term until June 30, 2002.⁸⁹

(12) Grievances lodged with the University

Dr. Olivieri and her supporters, Drs. Chan, Dick, Durie and Gallie, became members of the University of Toronto Faculty Association (UTFA) in late 1998. They reported to this Committee that they lodged written grievances with the University under the terms of the Memorandum of Agreement.* The Faculty Association lodged a related Association grievance. The grievances alleged infringement of these individuals' rights by the Hospital and failure by the University to exercise obligations (under the Memorandum of Agreement and under the affiliation agreement with HSC) to act to rectify the situation.⁹⁰ The grievances were later amended to add further allegations as events unfolded in 1999.

There is some overlap between the subject matter of the grievances and our terms of reference, but our task is independent of the grievances. There is an issue of procedure relevant to our discussion. Under the Memorandum of Agreement, a Grievance Review Committee can render a final and binding decision. A Grievance Review Committee is selected for a given case from the Grievance Review Panel "appointed by the President of the University after consultation with the Association." The practice has been that the President and the Association endeavour to reach agreement on both the Chair of the Panel (who may also chair a Committee) and on the person who is to provide legal and procedural advice to a Committee. Although the wording of the Memorandum of Agreement gives the President the authority to decide, there has been a willingness to discuss potential conflicts of interest on the part of proposed Panel Chairs or legal counsel for Grievance Review Committees. In the present instance, for many months there was no agreement on a Chair. After agreement on a Chair had been reached, there was no agreement on a legal advisor for the Committee until the fall of 2000. As a consequence, for over two years after they were lodged, no hearings had been held on these grievances. Hearings only commenced in late February 2001.

It is common at other universities to have in place a procedure for breaking such impasses in a timely manner. For example, at universities where grievances may be arbitrated under provincial labour codes, either party may appeal to the Minister of Labour to appoint a person to chair an arbitration board. Alternatively, a list can be agreed upon in advance, along with an automatic rule for breaking any impasse over selection from the list. The parties to the Memorandum of Agreement should consider an amendment to provide a mechanism for breaking impasses such as those that have occurred here, which delay any resolution.

*This is the document governing terms and conditions of employment for faculty members, an agreement between UTFA and the University, in force since 1977, with subsequent amendments.

(13) The settlement of January 25, 1999

We have described (section 5M) HSC's removal of Dr. Olivieri from her position as Director of the Hemoglobinopathy Program on January 6, 1999. Although the University was given notice two days in advance of this action, she herself was given no notice. When informed of the planned action on January 4, President Prichard had objected to the process the Hospital intended to use (summary removal, with no opportunity to answer the case against her) and had explained the requirements of due process to the Hospital President, Mr. Strofolino.⁹¹ He came away from their discussion believing that the Hospital had accepted his procedural advice. President Prichard also believed he had "received assurances that the proposed action would not impair her academic rights including her ability to conduct her research." The President learned on the evening of January 6 that his advice was not taken.⁹² Earlier that day, Dr. Olivieri had been summarily removed with no opportunity whatever to meet the case against her. Her academic rights were further impaired by a "gag order" letter issued concurrently with the dismissal. It was also accepted, later, that being deprived of the authority of the directorship impaired her ability to conduct her research (see terms of the January 25, 1999 settlement, in Appendix E).

Dr. Olivieri contacted UTFA, and association officers immediately took up her case in responding to the two letters Dr. O'Brodovich delivered to her on January 6 (one removing her from her directorship, the other curtailing her right to speak out). Following a meeting of the University-Association Joint Committee on January 11, the University set out in writing to UTFA its disapproval of the Hospital's unfair procedure both in removing Dr. Olivieri as director and in issuing the "gag order." During this meeting, the Faculty Association had asked that the University make efforts to have Dr. Olivieri reinstated immediately, pending a review of the circumstances, so that her research would not be disrupted. The University replied that it did not have the authority to over-rule the Hospital. In the same meeting the Faculty Association informed the University that the affiliation agreement between the University and the Hospital had expired at the end of December. "This had come as some surprise to the Provost and Dean Aberman."⁹³ The Association proposed that renewal of the affiliation should be tied to Dr. Olivieri's reinstatement, and to improvements in Hospital procedures affecting professors. The University refused, and instead promptly renewed the affiliation for one year. However, in his January 12 letter to UTFA President William Graham, Provost Sedra expressed willingness to meet with Dr. Olivieri so that she could "give the facts which support her claim that her ability to do her research ha[d] been adversely affected by the HSC action."⁹⁴ This claim was disputed by the Hospital.

A meeting was convened on the evening of January 20 so that Dr. Olivieri could explain to the University the adverse impact of her dismissal as director on her research work. Among those in attendance were the President of the University, the Provost, the Dean, the President and the Grievance Vice-President of the Faculty Association, and lawyers representing the University, the Association and Dr. Olivieri. Dr. Olivieri made a detailed presentation and answered many questions.⁹⁵ The University then proposed that a review of the situation by a third party be instituted. This was essentially the same proposal the Dean had made earlier in January, “that a senior clinician from our faculty be asked to review the conflicting facts” concerning “the nature of the impediment to her research and report to him”, and that this person would be someone “agreeable to both Dr. Olivieri and [the Dean].”⁹⁶ This proposal was again not accepted, as such, on the grounds that a member of the Toronto faculty might not be sufficiently independent, and that the reviewers should be persons who were internationally recognized authorities in hemoglobinopathies. The next day, Professor Graham wrote to President Prichard saying that Dr. Olivieri would accept a third party review, provided that the reviewer(s) were acceptable to her and were recognized experts in her field. Professor Graham proposed a list of five names from England and the United States from which a review committee could be struck.⁹⁷

At about the same time (on or about January 20), in his other capacity as President of CAUT, Professor Graham had written to the five experts to invite them to serve as reviewers of the hemoglobinopathy program at the University.⁹⁸ Four of them, Drs. Nathan (Harvard), Porter (London) and Schechter (NIH), and Sir David Weatherall (Oxford) confirmed their availability to come on short notice. Medical staff and administrators of HSC and TTH were invited to meet with the reviewers to discuss scientific aspects of the hemoglobinopathy program at the University. On learning of this development, President Prichard contacted Sir David with concerns that the University had not agreed to the composition of this review committee, and that Sir David and Dr. Nathan “had taken a clear and outspoken position in support of Dr. Olivieri but nevertheless the President hoped to benefit from their very considerable expertise.” Sir David and Dr. Nathan then withdrew from the CAUT program review and “proposed to come to Toronto at their own expense to attempt to resolve Dr. Olivieri’s concerns.”⁹⁹ Sir David and Dr. Nathan arrived on Sunday, January 24 to try to assist in resolving the dispute, while Drs. Porter and Schechter also arrived that weekend to conduct the CAUT program review.¹⁰⁰

Sir David and Dr. Nathan met with President Prichard and Dean Aberman on January 24. During the discussion, the President said he was prepared to entertain proposals for resolution.¹⁰¹ Already, during the Academic Board meet-

ing of January 21, in response to questions by a member, he had indicated he had understood important points of Dr. Olivieri's presentation the evening before.¹⁰² Dr. Nathan has reported in several contexts that he credits a telephone call to President Prichard by former Harvard President Derek Bok with increasing President Prichard's receptiveness to dealing at this time with Sir David and himself, since their interventions earlier in January had been ineffective.¹⁰³ It was agreed that President Prichard, Dr. Nathan and Sir David would work together to try to effect a resolution.

The fundamental points for Sir David and Dr. Nathan were that conditions should promptly be created to enable Dr. Olivieri to return to her internationally significant work, with adequate authority and resources to enable her to carry out her research projects. This included clinical authority over treatment of patients in research trials. As Dr. Nathan has explained it:

You can't do clinical research, ethically or technically, unless you are in charge of the patients. Trial conditions must be centrally enforced. Such work is impossible otherwise.¹⁰⁴

Sir David and Dr. Nathan felt that administrative and personal aspects of the disputes should be put aside in the interests of medical science.

Meetings were arranged for Monday, January 25 among representatives of the various parties, including HSC Board Chair Pitblado and HSC President Strofolino. Later that day mediation discussions were organized, involving Dr. Olivieri, representatives of the Hospital, the University, UTFA and CAUT, and lawyers for all parties, with President Prichard, Sir David and Dr. Nathan acting in mediative capacities, and with the lawyers providing advice on wording. Discussions began with Sir David and Dr. Nathan enunciating the general principles noted above. In the early hours of January 26 a settlement was reached. Dr. Olivieri, Sir David, Dr. Nathan, and representatives of CAUT and of UTFA who were involved in this long day all have credited President Prichard with having played a pivotal role in the successful outcome. The terms of the settlement were recommended to Dr. Olivieri and Mr. Strofolino by Sir David and Dr. Nathan in a letter.¹⁰⁵ The agreement was signed by Dr. Olivieri, Mr. Strofolino and President Prichard (it was dated January 25, but was not executed until about 2:00 AM on January 26).¹⁰⁶

The agreement was written in the form of a letter from the President to Dr. Olivieri and Mr. Strofolino that they were invited to co-sign. It contained sixteen numbered provisions and opened with the paragraph:

Reflecting our shared commitment to ensuring both that Nancy can continue her important work and that the Hospital for Sick Children can continue to advance its important mission, and in the interests of a comprehensive resolution of the matters that have divided you, I recommend a resolution in the following terms. In doing so I have been advised that Dr. Olivieri will retain

her current appointment in the Toronto Hospital as the Director of the Haemoglobinopathy Program and Director of the [University] Department of Medicine's Haemoglobinopathy Program.

The significance of the agreement is such that we have included a complete copy in Appendix E, but for purposes of this section we discuss only a few of its provisions. In it, Dr. Olivieri's reporting relationship was changed, so that her primary department would henceforth be Medicine and her cross-appointment would be in Pediatrics, the opposite of what they had been previously. Her office would be moved to The Toronto Hospital (TTH) and she would report to Dr. Baker (TTH Physician-in-Chief) in regard to both TTH and HSC duties. She would remain on staff at HSC and would continue to chair and lead the weekly clinic meeting at HSC and "have full access to and full responsibility and accountability for all [HSC] haemoglobinopathy patients' medical care subject to ethical and HSC policies and practices." Her position as program director at HSC would disappear and no similar position would be created. She would "remain a Senior Scientist in the [HSC] Research Institute." The two letters of January 6 from Dr. O'Brodovich (the letter of dismissal and the "gag order") would henceforth "have no continuing force and effect." HSC would continue to provide her programs with resources at the January 1999 level¹⁰⁷ and Dr. Baker would be consulted on staffing of her HSC clinic. By this means, the impairment to Dr. Olivieri's ability to carry out her research and clinical work caused by the dismissal was removed, and the sources of personal friction between her and HSC administrators were reduced by having her report to HSC through Dr. Baker.

It is of note that there was a provision that HSC would withdraw any restrictions on "the exercise of academic freedom by any member of the University faculty." The inclusion of this provision was in response to the "gag orders" issued on January 6 to Drs. Chan, Durie and Gallie, in addition to Dr. Olivieri. The wording signifies an acceptance by all three parties to the agreement, that faculty members working at the Hospital are entitled to academic freedom.

There were two provisions on legal matters. In clause 9, HSC agreed to "indemnify Dr. Olivieri for actual legal and other expenses incurred to date to a maximum of \$150,000." This sum was for legal representation in situations not covered by CMPA. Further, clause 8 provided that, if Apotex were to commence legal action against her for any matter occurring before January 25, 1999 and CMPA refused coverage, "HSC will pay her costs of defending such an action. In the unlikely event that Apotex were successful, HSC agrees to indemnify Dr. Olivieri with respect to any award or judgment." There are several noteworthy aspects to these provisions. For instance, the sum agreed

upon shows that in the absence of adequate internal structures for resolving employment disputes, employees who feel they must engage private counsel can incur expenses that are personally ruinous. The contents of clauses 8 and 9 provide tacit recognition that an individual could be financially ruined by a large corporation with deep pockets in pursuit of its commercial interests.

Another noteworthy phrase is, “In the unlikely event that Apotex were successful.” This appears to suggest a different prospect from that held out by the Hospital’s legal counsel, Borden & Eliot, in the fall of 1997: “The Apotex non-disclosure clause... was probably enforceable.”¹⁰⁸ Legal counsel for all parties were available and were consulted during the January 25 resolution discussions. (See in this connection the opinion of Professor D.A. Soberman on the common law concerning contract clauses which offend public policy, in Appendix F.)

Clauses 8 and 9 also imply acknowledgment by both the Hospital and the University of the fact that Apotex’s legal warnings to Dr. Olivieri had not been rescinded and she was still subject to possible legal action by the company for disclosures of data from the Toronto trials. These clauses also imply acknowledgement that Dr. Olivieri had rights as a clinical professor that might not have the protection of CMPA coverage when she exercised them. In contrast, the Hospital and the University had previously given the Naimark Review the impression that once CMPA had become engaged, this was quite sufficient and so their institutions had no obligation to provide legal support.

The agreement ended with important general understandings,

Beyond the specifics of this recommended resolution, I [President Prichard] want to record my understanding of your shared commitment to making all of this work. It will require effort and growing good will from everyone concerned.... I am very grateful to both of you and your colleagues for your willingness to embrace this resolution in the interest of moving forward together. Please indicate your consent to this resolution by signing this letter.

Dr. Olivieri and Mr. Strofolino then duly signed, with the benefit of legal advice from their respective advisors.

There is much to be said in favour of this document, and much to be said about the skill and energy of President Prichard, combined with the moral authority of his office, in helping to bring about such a resolution. It must be noted, however, that he did not intervene effectively until UTFA and CAUT unilaterally invited Sir David Weatherall and Dr. David Nathan to come to Toronto. The scientific eminence and administrative experience of these two co-mediators were vital, not only to the success of the mediation discussions, but to the initiation of the process. Further, it is reasonable to infer that if the

University and the Hospital had provided the same support for Dr. Olivieri in the summer of 1996 as provided for in the 8th paragraph of the resolution, then the dispute with Apotex might not have escalated as it had in the ensuing two and a half years. Nevertheless, the January 25 agreement did present an opportunity for resolution of what had become a very complex, contentious problem—provided it had been promptly and fully implemented.

(14) Failure of the settlement to resolve important matters

Events in the following months raised questions about the Hospital’s commitment to a basic purpose of the agreement, which was to reflect “our shared commitment to ensuring... that Nancy can continue her important work.” The Hospital took inappropriate actions against Dr. Olivieri and her program—actions that undermined clauses 12 and 13 of the agreement pertaining to resources and means of communication (see Appendix E).*

Problems with implementation of these aspects of the agreement began shortly after it had been executed. For example, on February 10, 1999 Dr. Olivieri left for a short period to work on a research project in Sri Lanka. The Hospital, without consultation, then terminated her telephone, voice mail and pager telephone services. It also ordered her research staff to leave HSC. These actions disrupted communications between Dr. Olivieri and her research fellow who was coordinating hemoglobinopathy patient care during her absence. Dr. Gallie learned of this and contacted Dean Aberman, who intervened to resolve this problem. The HSC administration later took additional adverse actions, such as removing from Dr. Olivieri and her staff the space they had been using for research and for administrative work pertaining to the care of HSC patients.¹⁰⁹ These developments were factors leading the President of the University to intervene again, in the summer of 1999.

(15) Mediation

The HSC colleagues who became Dr. Olivieri’s principal supporters, Drs. Chan, Dick, Durie and Gallie consider that they also have been subjected by the Hospital to unfair treatment in matters concerning their working conditions. There had been some preliminary discussion in late January

*Grounds for raising still more serious questions about the Hospital’s understanding of this “shared commitment” emerged only a year later. In December 1998, the Hospital had directed the Medical Advisory Committee to review aspects of Dr. Olivieri’s conduct. The MAC then received new allegations in December 1998 and early 1999 that provided the basis of further actions against her, but did not disclose these new allegations to her. These allegations were not disclosed until a year later. (See section 5P.)

1999 to the effect that a mediated agreement might be required so as to resolve their concerns. During the first half of 1999, additional concerns arose regarding the employment conditions of all four of these individuals due to actions by Hospital administrators. Also, as noted above, problems regarding implementation of some terms of the agreement of January 25 concerning Dr. Olivieri had arisen. Representations to Hospital and University administrators were made during the first half of 1999, by Dr. Baker, by UTFa, and by lawyers for the five professors, but to no avail.¹¹⁰ However, there is evidence that the University accepted that there was some validity to these claims, as we now explain.

The last of the sixteen clauses in the agreement of January 25 stated that, in the event of “disputes with respect to implementation..., HSC and Dr. Olivieri agree that the President of the University of Toronto will mediate such disputes.” In early August 1999, Dr. Baker drafted a framework for a mediation process to bring about a settlement on a range of issues. In late August, the five professors, their legal counsel and Association officers met with President Prichard, Dean Naylor, other University administrators, and Dr. Baker to discuss the outstanding issues and a process for resolution. President Prichard then asked Dean Naylor and Dr. Baker to try to mediate between the professors and the HSC Executive. Initial efforts were unsuccessful. In another meeting, in October, President Prichard suggested that the five professors and HSC should consider accepting Dean Naylor as an arbitrator who would impose a settlement after hearing all parties. This proposal was not accepted by the Hospital.¹¹¹

President Prichard next proposed that Dean Naylor resume mediation efforts. Discussions involving Hospital representatives and the five professors, mediated by Dean Naylor, recommenced in mid-October. Through Dean Naylor’s efforts, by mid-December a document had been developed, and the professors and Mr. Strofolino were invited to sign it to signify their acceptance of the terms of the proposed settlement. We have been told by participants in the process that there is much to recommend this document, and that a great deal of effort and diplomatic skill had been devoted to the process by Dean Naylor. However, to date, the proposed document has not been signed.

(16) The delay in completing mediation

The reasons that the mediation document has not been signed appear to relate more to the wider context, than to terms in the document itself. By mutual agreement, the mediation process did not deal with some important matters about which there was a high level of concern, both on the part of

the five professors and of the Hospital administration, although for different reasons. These matters included the MAC investigation into Dr. Olivieri's alleged "failure" to report L1 toxicity to the REB, and the Hospital's investigation into misconduct allegations against Dr. Koren. Both had potentially serious implications. In the view of the five professors, the proposed mediation settlement required good faith on the part of all intended signatories. By mid-December they felt they had reasons to doubt the Hospital's ultimate intentions. These arose from the Hospital's response to DNA evidence that Dr. Koren was guilty of misconduct and was lying to cover it up.

The MAC proceedings are discussed in section 5P, and Dr. Koren's misconduct is discussed in section 5R. The latter was of immediate concern in December 1999, because of the DNA identification of Dr. Koren. The five professors told this Committee that this was a significant factor in their decision to delay signing the mediation document, so we briefly review it here. A series of anonymous letters disparaging Drs. Olivieri, Durie, Chan and Gallie had been issued between October 1998 and May 1999. They reported they found these letters deeply disturbing and the delays in action in regard to them no less disturbing. They had lodged a formal complaint in May 1999 identifying Dr. Koren as the author, based on substantial evidence compiled a private detective and analysed by forensic experts. Dr. Koren denied any involvement. The Hospital then hired its own investigator, Ms. Barbara Humphrey. Her investigation continued for many months, in part because it had been "frustrated" and "obstructed" by a series of "lies" Dr. Koren told her.¹¹²

On December 7, 1999 when all but final details of the proposed mediation agreement were in place, the five professors obtained additional forensic evidence, in the form of matching DNA samples, that Dr. Koren was the author of the anonymous letters.* They and UTFA presented this information to the University and to the Hospital on December 8 and asked for action against Dr. Koren. Provost Sedra replied for the University of December 9, saying that "any consideration of discipline will have to await [Ms. Humphrey's] report."¹¹³ The Provost added, "We have been given assurances by the Hospital that the report of the investigator will be completed prior to the end of December." Ms. Humphrey was provided with a copy of the DNA report on December 10.¹¹⁴ Mr. Alexander Aird, Chair of the Board of Trustees, res-

*The matching DNA was obtained from saliva residues on (i) envelopes of anonymous letters attacking Dr. Olivieri and her supporters, and (ii) the envelope of a hand-written and -addressed letter in Dr. Koren's handwriting that he had sent to his long-time acquaintance, Dr. Michèle Brill-Edwards. (See section 5U.) The analysis was conducted by forensic experts at the Helix Biotech laboratory in Richmond, BC.

ponded for the Hospital on December 10. In his letter to Dr. Chan *et al.*, he said:

[T]he investigator retained by the Hospital... will be reporting soon. *I would therefore urge you not to take any unilateral steps which might damage the reputation of one of your colleagues.*¹¹⁵ (emphasis added)

The five professors told this Committee that for several reasons, Mr. Aird's concern for Dr. Koren's reputation served to heighten their concerns that no significant action would ever be taken against Dr. Koren. First, on September 1, 1998, without investigation, the Hospital had publicly repeated allegations potentially damaging to Dr. Olivieri's professional reputation that had been made privately to the Hospital by Apotex (see section 5L).¹¹⁶ Second, an unmistakable purpose of the anonymous letters was to damage the personal and professional reputations of Drs. Olivieri, Chan, Durie and Gallie, who now considered they had conclusive proof that Dr. Koren was the author. Third, the Hospital had taken no significant action in regard to other alleged misconduct by Dr. Koren (Dr. Olivieri alleged that he had provided false information to the Naimark Review, which had been relied upon by that review in finding against her.¹¹⁷) Dr. Olivieri and her colleagues reported to us that Mr. Aird's concern for Dr. Koren's reputation suggested to them that there was a double standard regarding personal and professional conduct.

Information that DNA evidence identified him as the author of the anonymous letters was conveyed to Dr. Koren on or about December 10.¹¹⁸ Approximately a week later, Dr. Brill-Edwards authorized Dr. Olivieri to make the original of Dr. Koren's hand-written letter and hand-addressed envelope available to the Hospital and the University, and Dr. Koren admitted responsibility. On December 20, HSC President Mr. Strofolino informed the press that the author of the anonymous letters had been identified and this information was published in the *Toronto Star* on December 21, "The individual has confessed to authoring the letters," says... Michael Strofolino." The *Star* added, "Strofolino did not name the individual, but confirmed he had been a key suspect." However, it appears that the identity of the individual had been communicated to other newspapers on or before December 20, because both the *Globe and Mail* and the *National Post* articles of December 21 said that Dr. Koren was the author of the anonymous letters. When Mr. Strofolino spoke to the press on December 20, Ms. Humphrey's investigation was still not complete, but rather "virtually complete," the *Star* reported on December 21. Ms. Humphrey's report was made available to the press on December 21, and she told reporters that,

“she concluded Koren was the culprit by comparing the use of language in the letters to articles Koren has written.”¹¹⁹ *

The Hospital and the University announced on December 21 that Dr. Koren would be suspended with pay, pending a disciplinary hearing.¹²⁰ It was on December 21 that Dr. Dick wrote to Dean Naylor to advise that he and his colleagues were “unable to deal with [i.e., sign] the [mediation] agreement at the present time,” as a result of uncertainty arising from recent developments.¹²¹

For the next several months, the presidents of the Hospital and the University, Dean Naylor, and Dr. Olivieri, her four colleagues and UTFA were considerably occupied with disciplinary proceedings concerning Dr. Koren’s misconduct. He was provided with due process: he was represented by legal counsel, he and his counsel were provided with all information against him, and he had an opportunity to challenge this information and respond to it. On April 11, 2000, penalties were imposed on him. (See section 5R.)

Two weeks later, on April 27, 2000, the Hospital took significant action against Dr. Olivieri in a highly public manner that was damaging to her reputation: it referred a report by the MAC to external bodies. Dr. Olivieri had been denied due process in the MAC investigation. The MAC relied on incorrect information from Dr. Koren, as well as information from others that was incorrect, but this information was not disclosed to her. This action by HSC further deflected attention from the mediation process.

It is possible that Dean Naylor’s settlement proposal of mid-December 1999 could still result in a fair resolution to many outstanding issues, provided it were not only signed by the parties, but accompanied by a clear demonstration that it would be fully and promptly implemented.

*Dr. Olivieri *et al* had provided similar comparisons by forensic experts (a document examiner and a linguist) to the Hospital and the University in May and June 1999. (See section 5R.)

(17) The University's response to complaints against Dr. Koren

In the late spring of 1999, Dr. Olivieri *et al.* provided the Hospital and the University with a substantial body of evidence from forensic experts identifying Dr. Koren as the author of the series of anonymous letters against them. He denied responsibility. The author of these letters had committed serious violations of University policy, in addition to Hospital policy. This forensic evidence might have been sufficient for many employers to have taken disciplinary action against him.¹²² The Hospital decided instead to institute its own forensic investigation and retained Ms. Barbara Humphrey to conduct it. The University, for its part, left the matter in the hands of the Hospital. The University's inaction in the face of the allegation that Dr. Koren was the author and the substantial supporting evidence is hard to understand. It apparently made no attempt either to retain its own investigator, or to arrange for Ms. Humphrey to extend the scope of her investigation to consider matters relating specifically to Dr. Koren's responsibilities as a professor (for example, not to infringe the academic freedom of his colleagues). Ms. Humphrey noted in her report that, although Dr. Olivieri *et al.* alleged that Dr. Koren breached "responsibilities that he held as a Professor... at the University...", she had been "retained to conduct an investigation on behalf of the HSC [only]..." and so, "[University] issues have neither been identified nor addressed in this report."¹²³

The University and the Hospital eventually took disciplinary action against Dr. Koren in April 2000, but only after he admitted to misconduct. His admission followed additional effort and expense by the persons who were the victims of his "hurtful"¹²⁴ misconduct, who obtained the DNA evidence that he was guilty. When the institutions eventually imposed disciplinary sanctions on him, these were limited, even though the presidents of the University and the Hospital found that his actions "...constitute gross misconduct and provide sufficient grounds for dismissal."¹²⁵ It is also significant that the University and the Hospital disciplined Dr. Koren only for misconduct to which he admitted, directly or indirectly.¹²⁶

(18) The University & Apotex

As outlined in section 4 of this report the University and Apotex had been engaged in discussions on a possible major donation since 1991. Agreement in principle on the major donation was reached in the spring of 1998. In the fall of 1998, after the L1 controversy had become the subject of widespread media attention, the University and Apotex agreed that discussions to finalize the donation “should be suspended until the matters in dispute were resolved” and “Apotex should be cleared of wrongdoing,” as the minutes of the December 17, 1998 meeting of the University’s Governing Council record.¹²⁷

The minutes of the Governing Council meeting gave no indication as to the means by which “Apotex should be cleared of wrongdoing,” or “the matters in dispute” should be “resolved.” The Naimark Review, whose report had been publicly released a week earlier, did not address the question of possible wrongdoing by Apotex in relation to its actions against Dr. Olivieri, a professor in the University “entitled to the full freedoms, rights and privileges of all members of the faculty including vigilant protection of her academic freedom.” (See sections 5N(1), 5N(8) and 5O.) Nevertheless, in public statements, the University relied on the Naimark Report to suggest that, even though Apotex had used legal warnings in attempts to impede Dr. Olivieri in exercising her academic rights and fulfilling her ethical obligations, intervention by the University had resolved this problem. An example is the article in the December 14, 1998 issue University’s newsletter, *The Bulletin*, quoted earlier (section 5N(1)). President Prichard made a similar statement on December 9, 1998:

Dr. Naimark’s report documents the intervention of Dean Amie Aberman and other senior university officials to protect Dr. Olivieri’s rights as a clinical faculty member.¹²⁸

The Naimark Report correctly noted that Dean Aberman had intervened with the goal of protecting (“to protect”) Dr. Olivieri’s rights, but it did not say that these interventions were successful in essential respects. Indeed the Report noted that the Apotex legal warnings continued and had not been rescinded.¹²⁹ The Report also noted one of the several instances when Dr. Olivieri withdrew an abstract already submitted to a conference, in response to Apotex legal warnings.¹³⁰ Although it was well documented in Apotex correspondence provided to the Naimark Review that the company had repeatedly infringed Dr. Olivieri’s academic rights, this matter was not addressed in the Report. In summary, we are not aware of any investigation in 1998 (or earlier) of what was referred to in the Governing Council minutes as possible “wrongdoing” by Apotex.

The other pre-condition for lifting the suspension of discussions on the proposed major Apotex donation was that the matters in dispute should be

resolved. The Naimark Report did not resolve any of the matters in dispute and the public controversy continued. New matters of dispute arose in December 1998 and thereafter. Some matters were resolved through the agreement of January 25, 1999 but as discussed in various sections of this report (for instance, sections 5P and 5Q), others were not resolved.

It is not clear in what manner or to what extent the University regarded the matters in dispute as being resolved, or Apotex cleared of wrongdoing. The suspension of discussions on the possible major donation by Apotex was lifted in 1999 (see section 4).

(19) Conclusions

1 | In December 1998, the University made public statements strongly supportive of Dr. Olivieri's rights. On December 14, 1998 President Prichard said, "The University's pre-eminent obligation is to ensure the academic freedom of all of its members, wherever they work."¹³¹ The University's twelve-point statement of December 3 said, "Dr. Olivieri is entitled to the ... vigilant protection of her academic freedom," and, "we will protect the full rights, privileges and freedoms of our faculty members."¹³² In this statement the University also claimed that it had protected her academic freedom, because "in 1996 the Dean of Medicine successfully intervened at the request of Dr. Olivieri to mediate ... and achieved with the consent of both Apotex and Dr. Olivieri the disclosure of Dr. Olivieri's scientific data."

However, the University was not successful in protecting Dr. Olivieri's academic freedom and other rights. To summarize:

Dean Aberman asked officers of Apotex in 1996 to desist from their legal warnings to Dr. Olivieri. The legal warnings continued, and he was copied on a number of them so it should have been clear that his interventions to this end were not effective. The legal warning letters have not been rescinded. Dr. Olivieri informed the regulatory agencies and the scientific community with the legal support of the CMPA. The extensive involvement of CMPA legal counsel in 1996 and 1997 serves as an independent demonstration that Dr. Olivieri's academic rights were not being protected by the University.

"[T]he University had a very good relationship with Apotex through its owners,"¹³³ but no effort that was effective was made by any officer of the University, or by the University as an institution, to persuade Apotex to stop issuing legal warnings to Dr. Olivieri not to disclose information on risks of its drug. In particular, Apotex's Vice-President, Dr. Spino repeatedly

infringed Dr. Olivieri’s academic freedom, unchecked by the University in which he still continues to have the status of professor.

Concerns brought in 1997 to Dean Aberman by several scientists, that Dr. Olivieri was not being provided with adequate assistance by either the University or the Hospital, were not accepted by him.

Although Apotex had been infringing the academic freedom of one of its professors, Dr. Olivieri, and academic freedom is a pre-eminent concern of the University, it took the view that the dispute was primarily the concern of the Hospital. The University did not ensure that there would be an independent review or that the Hospital’s review would address academic freedom.

2 | Immediately upon receipt of the Naimark Report in late 1998, the Hospital instituted an adverse action against Dr. Olivieri by establishing the MAC inquiry into her conduct. We have no evidence that this action was reviewed with the University prior to such action taking place, or that the University raised any objection, or interceded in an effort to ensure due process would be provided to Dr. Olivieri after the Board’s public announcement of its action.

3 | The Hospital did consult President Prichard prior to removing Dr. Olivieri from her directorship, but it did not follow his advice on the provision of due process. The University acted to remedy this situation after eminent medical scientists from Oxford and Harvard, along with officers of UTFA and CAUT advocated this.

4 | President Prichard did not include academic freedom in the terms of reference he provided Professor Dickens for his review in regard to policy harmonization with the teaching hospitals.

5 | Despite the substantial forensic evidence available in May 1999 that Dr. Koren had violated University norms of conduct, the University did not conduct its own investigation into alleged misconduct by him, and did not arrange for the Hospital’s investigator to consider University policy, and did not act against him until after he admitted his guilt.

6 | Although there were failures by the University to act effectively in regard to Apotex’s legal warnings against Dr. Olivieri until January 1999, thereafter it played an important role and effectively assisted Dr. Olivieri in a number of respects.

7 | Dean Aberman made a substantial and effective intervention in June 1996 when he mediated the reinstatement of the supply of L1 under a new

EDR arrangement, after Apotex abruptly terminated the trials and withdrew its drug from the HSC pharmacy. He intervened again later that year when Apotex stopped the supply of its drug a second time.

8 | The announcement by Dean Naylor on March 26, 2001, that the University and its affiliated teaching hospitals had agreed to make substantial improvements in their publication and other research policies, could constitute a very important advance, if the changes are fully and effectively implemented. In view of the prominence of the University of Toronto and its affiliated hospitals in medical research in Canada, this could lead to policy improvements at other universities and hospitals.

This change in policy shows that the previous publication policy, with which both contracts for the Toronto L1 trials were in compliance, was inappropriate for clinical research.

9 | The mediation process undertaken by Dean Naylor in late 1999 made substantial progress and this might still form the basis for resolution of a number of important outstanding issues.

5.0.1. The Process

(1) Establishment of the Review

BY THE SUMMER OF 1998 the disputes involving Dr. Olivieri, Apotex, the Hospital for Sick Children, and the University of Toronto had been ongoing for more than two years, and increasing numbers of HSC medical and scientific staff expressed concerns. The controversy reached a wider public with the publication of Dr. Olivieri's paper in the *New England Journal of Medicine* on August 13.¹ Intense media scrutiny added to pressure from within the institution for an independent inquiry.

Initially, the Hospital's Board of Trustees announced it would have a review of policies and procedures governing clinical trials, a review that would not deal with the L1 matter specifically.² This was not well accepted in some quarters. The Board then agreed to establish a two-phase review, the first on the controversy, and a later one on policies and procedures. On September 8, 1998 the Board of Trustees established the first phase of the review, giving it a mandate:

to determine the facts and circumstances giving rise to the current controversy... including matters pertaining to the following: Patient Safety at the Hospital for Sick Children; Conflicts of Interest; Release and Publication of Research Information.³

The Board appointed Dr. Arnold Naimark to conduct this phase of the review and report by November 30.⁴ He immediately began conducting interviews and collecting documents.

(2) The Reviewer & his associate reviewers

Further controversy ensued because Dr. Olivieri and her supporters were not consulted on the selection of Dr. Naimark. Some objected that there was a reasonable apprehension of bias in the reviewer, since Dr. Naimark had raised money from Apotex while President of the University of Manitoba,⁵ and was a member on the Board of Directors of the Canadian Imperial Bank of Commerce (CIBC). The Chair of the CIBC Board, Mr. A.L. Flood was a member of the Board of the HSC Foundation and the CIBC was active in fundraising for Hospital projects. Others (including Nobel laureate Dr. John Polanyi) raised the concern that, regardless of the individual appointed, it was unusual for a single person to be asked to review such a complex matter.⁶ These concerns were expressed in a motion passed by the HSC Medical Staff Committee on September 17, and approved by a majority of

those present at general meeting of the Medical Scientific Staff Association on October 1:

That the Medical Scientific Staff Association (MSSA) make representation to the Board of the Hospital for Sick Children, stating that *the process* of the Independent External Inquiry into all aspects of the Apotex Affair *must be open, consultative and independent. Full disclosure* of all information heard by the reviewers will assure that the process is open. *Three or more reviewers* with relevant expertise, *chosen by consultation* between the parties, will insure that the process is independent.⁷ (emphasis added)

These representations led to considerations of enlarging the review panel, and in late September 1998 Dr. Naimark began discussions with the interested parties at HSC on the prospects of adding one or two persons to assist him in the review. Dr. Olivieri and her principal supporters (Drs. Chan, Durie, Gallie and Dick) had discussions with him directly and through intermediaries in the hope of reaching agreement with him and with the Board on one or two persons to join him. This led to the possibility in late September and early October that Dr. Patricia Baird might accept Dr. Naimark's invitation to assist him in his "capacity as the Reviewer."⁸ In correspondence with Dr. Naimark, Dr. Baird agreed to accept provided he could assure her:

that in the event that I am not in agreement with your review report, I would have the opportunity to add my own section to the report that goes to the Board and is disseminated.⁹

Dr. Naimark replied that he had consulted with the Chair of the Board and was advised that any arrangements other than receiving one reviewer's report were not desired.¹⁰ He offered instead the possibility of considering "the inclusion of annotations (with attribution)."¹¹ Dr. Baird then declined the invitation for the reason that this would not provide her with appropriate independence.¹²

Subsequently Dr. Henry Friesen, President of the Medical Research Council (MRC), was asked to mediate between the Board and Dr. Olivieri and her supporters, to assist in finding mutually agreeable persons to join Dr. Naimark and to put in place conditions for their participation. A "Participation Agreement" negotiated on October 19 contained several "accommodations," including:

- two associate panellists to be chosen by the Reviewer [Dr. Naimark] from a list prepared by Dr. Henry Friesen with the concurrence of the Board and Dr. Gallie *et al.*
- the associate panellists ... will be at liberty to express in writing their concurrence or disagreement with any or all aspects of the report within the body of the final report and to sign the report.¹³

Also included was provision for extending the time for completion of the report. This agreement was signed only by Dr. Olivieri and her supporters, but on the express understanding that “the response provides for written acceptance by the Board.”¹⁴

In a situation by now fraught with suspicion and tension, there also was a mutual undertaking¹⁵ that the parties would cease public criticism of each other. HSC President Mr. Michael Strofolino wrote an e-mail memo to all medical and scientific staff asking that everyone “refrain from such activity,” but not until the afternoon of October 22.¹⁶ Unfortunately, public criticism of Dr. Olivieri by senior HSC staff continued on the day of the signing of the Participation Agreement and on subsequent days. For example, on October 19, Dr. Buchwald sent an e-mail to many persons outside the Hospital, endorsing a widely disseminated e-mail Dr. Sergio Grinstein had sent October 13 with a letter Drs. Buchwald and O’Brodivich had sent to *Nature Medicine* on October 14 enclosed (see section 5L(8)).¹⁷ Also, the first two in a series of anonymous letters against Dr. Olivieri and her supporters were sent out on October 20 and 21, one to a national newspaper.¹⁸ It was clear from the enclosures with the anonymous letter to the newspaper that its author had close contacts with the HSC Executive or Apotex, or both (more than a year later, after he had been identified by DNA evidence, Dr. Koren admitted responsibility for the anonymous letters—see section 5R).

The lists of names Dr. Olivieri and the Board selected from Dr. Friesen’s list did not intersect and efforts in late October to resolve this disagreement failed. On November 4, both the Board and Dr. Olivieri’s supporters announced the breakdown of the Participation Agreement.¹⁹

With his report due on November 30, Dr. Naimark selected two “associates” on November 12 from Dr. Friesen’s list to assist him in his review, Drs. Bartha Knoppers and Frederick Lowy, neither of them with the concurrence of Dr. Olivieri. Dr. Knoppers is an expert in health law and policy at l’Université de Montréal, and Dr. Lowy is Rector of Concordia University and a former Dean of Medicine in the University of Toronto. By the time Drs. Knoppers and Lowy actually became engaged in work of the Review, Dr. Naimark’s interviews were largely completed.* They were provided with his list of documents, access to the documents and his draft of the main sections of the report, and were asked for a critique and recommendations for revisions and additions.²⁰ The Naimark Report was released to the public by the Board on December 9.²¹ The Report was based on the investigation of one person,

*Dr. Naimark’s written progress report dated October 12, 1998 stated that “approximately 35 persons will have been interviewed by mid-October.” According to his final report (pp. 152–3) that was released December 9, 1998, 40 persons were interviewed or otherwise participated in the Review.

who had drafted the main sections. Indeed Dr. Naimark refers to himself in the Report as “the Reviewer.”²²

(3) The evidentiary base

The Report lists forty participants in the Review, the majority HSC administrative, medical and scientific staff. The list also included senior administrators of the University, a representative of Apotex, and others. Due to the breakdown in the “Participation Agreement,” Dr. Olivieri and her supporters did not participate, but Dr. Naimark reported he “worked almost exclusively from the written record,” and approximately half of the several hundred items of correspondence considered were “letters to or from Dr. Olivieri” or “communications written on her behalf.”²³ He added:

If, at any time, we come into possession of evidence which contradicts any material aspect of our Report, we feel honor-bound to report that to the Board of Trustees and to make that report public.²⁴

Dr. Naimark’s account implies the validity of his findings rests largely on the completeness and quality of the documentary evidence he had before him. Unfortunately, the Review was compromised in two material ways. First, some documents it relied on contained incorrect or false information. Second, the Review’s own records show that it did not have all of the relevant and important documents—there were critical omissions.

The “primary submitters” of information to the Review. To evaluate the reliability of the documents, sources as well as contents of must be considered. Two lists of the primary suppliers of material to the Review were made available a year after its Report was released, one given by Mr. Alexander Aird, Chair of the HSC Board of Trustees, the other by lawyer Ms. Barbara Humphrey who was retained by the Hospital to investigate allegations of misconduct against Dr. Koren.

Mr. Aird stated in a letter to Dr. Olivieri on December 30, 1999 that:

His (Dr. Naimark’s) conclusions relied primarily on correspondence and documentation originated by Dr. Olivieri and her supporters, the senior administration of the hospital and Apotex’s Dr. Spino.²⁵

Mr. Aird wrote this after Dr. Koren’s admission that he had been persistently dishonest with his employer and with his colleagues about anonymous letters against Dr. Olivieri and her supporters. Mr. Aird said that Dr. Naimark had been contacted following this admission and:

asked to indicate to what extent, if at all, Dr. Koren’s belated acknowledgment of responsibility for the anonymous letters affected the conclusions of the Naimark Review. Dr. Naimark has assured the hospital that his findings and

conclusions remain unaltered. Moreover, he made it clear that, contrary to your [Dr. Olivieri's] assertions, his review did not rely heavily on evidence supplied by Dr. Koren*.²⁶

A week earlier, another more detailed list of the suppliers of information to the Review from within the Hospital had been made available Ms. Humphrey. Her report included data on which of the many contacts listed by Dr. Naimark were the primary suppliers of information to him, citing Dr. Buchwald's testimony that "the primary individuals submitting to Naimark" were "Dr. O'Brodovich, Dr. Goldbloom and Dr. Koren" and that, in particular, Dr. Koren had "submitted 'a lot of stuff.'"²⁷ Ms. Humphrey found that Dr. Koren was systematically dishonest with her, inventing stories to obstruct and mislead her investigation into his conduct.²⁸ She found that some of his activities in regard to the anonymous letters were connected with material he submitted directly to Dr. Naimark, and some with discussions or correspondence he had with another of the "primary submitters," Dr. O'Brodovich.²⁹

This difference in perception on the influence and input of Dr. Koren is important. Dr. Koren is a central figure in the entire L1 controversy. In the voluminous correspondence among Drs. Olivieri, Koren, Spino, and O'Brodovich and other members of the senior HSC administration, Dr. Koren appears with great frequency, as author, addressee, or recipient of copies. His long-standing collaborations with Dr. Spino, his attempts to discredit Dr. Olivieri, his publications favourable to Apotex's drug, and his dishonesty to his employers and colleagues are relevant aspects of the dispute.

Ms. Humphrey had considerable experience in investigating workplace harassment. She examined the Naimark Report and much of its documentary base, and interviewed Dr. Koren and others, in order to ascertain the extent of Dr. Koren's knowledge of L1 matters and of the Naimark Review process. This was important for her investigation because, owing to his persistent denials, she wished to determine his knowledge of matters referred to (and appended to) the anonymous letters. She found that "Dr. Koren was the most constant individual at the center or the heart of the L1 trials controversies... All these issues appeared to have involved Dr. Koren in a very direct and personal sense."³⁰ She also found Dr. Koren to have been in association with and to have influenced Dr. O'Brodovich during the Naimark Review. Therefore, the statement that the findings and recommendations of the Review were not affected by Dr. Koren's involvement appears untenable. (See also section 5.O.2.)

*Possibly Dr. Naimark was not given a copy of the Humphrey Report and so may not have been aware of the extent of Dr. Koren's influence on Dr. O'Brodovich's testimony (see below).

Gaps in the Naimark Report archive deposited in the HSC library. The table of contents of the Naimark Report states that copies of correspondence cited would be placed in archives at the Hospital. In fact, less than half the items listed in Appendix 1 (Reference List of Documentation) to the report were deposited in the HSC library archives.³¹ We initially supposed that Dr. Naimark deposited all documents actually cited in the report, and only those, but this hypothesis was not confirmed by closer examination. For example, a long letter Dr. Spino wrote to Dr. Naimark on November 24, 1998 justifying the conduct of Apotex and criticizing the conduct of Dr. Olivieri was cited at page 101 of the Report and listed in the appendix, but was not deposited in the archives.³² At page 42 of the Report Dr. Naimark appears to have used information conveyed in two letters to him from Dr. O’Brodivich, one of which was listed but not deposited, the other neither listed nor deposited.³³ Another example listed but not deposited (and apparently used at pages 42 and 134) is a letter from Dr. O’Brodivich to Dr. Olivieri’s CMPA counsel dated March 3, 1996.³⁴

Furthermore, there are items listed in Appendix 1 of the Naimark Report, but not cited in the text of the Report and not deposited in the HSC archive, that are of such importance that it is hard to understand why they were not cited. The following are examples:

a) a memo from Dr. Koren to Dr. Buchwald, dated May 14, 1998, concerning his Apotex-funded research fellow, Dr. Orna Diav-Citrin and her work with patients who had been enrolled in the LA-03 trial. In this memo Dr. Koren (correctly) stated that this trial had been “discontinued” in “May 1996.”³⁵ Later in 1998 he put forward, both to the Naimark Review and to the Medical Advisory Committee inquiry, (incorrect) testimony that this trial had continued after May 1996. (see sections 5.O.2 and 5P).

b) several letters written by Dr. Koren in 1997 and 1998,³⁶ which contradict statements in two letters he alleged he sent to Dr. Olivieri in December 1996 and February 1997 but which she reports she never received.³⁷ Dr. Naimark reproduced the latter two in their entirety in the text of his report (page 41);

c) a letter Dr. Spino wrote to Dr. Koren on April 18, 1996 in which it was noted that Dr. Koren did not agree with Dr. Olivieri’s finding of a risk of the drug L1 (loss of sustained efficacy);³⁸

d) a letter Apotex’s legal counsel wrote to Dr. Olivieri’s CMPA legal counsel on December 18, 1996 and the reply by CMPA counsel on January 14, 1997. Apotex’s counsel wrote that at the ASH meeting in Orlando in early December 1996, Dr. Olivieri “implicat[ed] deferiprone in the development of hepatic fibrosis” in some patients. The CMPA counsel replied that Dr. Olivieri had not said that there was “causality between the administration of deferiprone and the

development of hepatic fibrosis” in patients, but rather that she had “presented data from previously published animal studies” and “then presented histologic findings in liver biopsies in patients” who had been in LA-03. He assured Apotex’s counsel that in the event any “safety concerns with respect to deferiprone” were to be identified, Apotex would be so advised.³⁹ The letter by CMPA counsel contradicts a conclusion in the Naimark Report that Dr. Olivieri had identified the risk that L1 could cause progression of liver fibrosis “by the end of 1996.”⁴⁰ (This risk was not identified until early February 1997—see section 5K.)

There is a very significant document that, while not listed in Appendix 1 of the Report, was deposited, but only in part, in the HSC library archive. It is a lengthy memorandum to Dr. Naimark by one of the “primary submitters,” Dr. O’Brodivich, dated September 24, 1998, in which he made allegations against Dr. Olivieri.⁴¹ The memo sets out in chronological point form an interpretive narrative of events that is incomplete and incorrect in important respects. Ms. Humphrey later reported that “in all likelihood the memo was prepared with input from Dr. Koren.”⁴² Sections II and III of the memo are in the archive, but not section I. (We do not know whether the memo had additional sections.) Section III is entitled, “Olivieri’s Failure to Follow the Guidelines for Research involving Human Subjects,” and it contains an (incorrect) account of events in 1997 in support of this allegation of failure. The allegation was believed by the Naimark Review panel, on the basis of incorrect testimony put forward during the Review by Dr. O’Brodivich, Dr. Koren, Dr. Moore and Dr. Spino, including some testimony in Dr. O’Brodivich’s memo of September 24, 1998.

This September 24, 1998 memo of Dr. O’Brodivich was also judged by persons adversely affected by Dr. Koren’s conduct to be material evidence in two subsequent proceedings. One was the inquiry by the Medical Advisory Committee (MAC) on Dr. Olivieri’s conduct. The other was the disciplinary proceeding before a panel of senior University and Hospital administrators on the admitted misconduct of Dr. Koren. Dr. Koren had appended the contents of one of the missing pages of the O’Brodivich memo (page 3 of section I) to the first of his anonymous letters, the one sent to a newspaper on October 20, 1998. However, in spite of the relevance and importance of the complete submission of Dr. O’Brodivich, access to it has not yet been given by the Hospital, or by its author. The responses to repeated requests by Dr. Olivieri and her legal counsel for access to the complete document suggest that the contents of the missing pages are significant.*

*In the initial response to a request by Dr. Olivieri for a complete copy of Dr. O’Brodivich’s memo, on December 30, 1999 legal counsel for the Hospital provided one of the missing pages, page 3 of Section I. This is the page, the paragraphs of which Dr. Koren had rearranged by cutting

(4) Missing documents

There are highly relevant documents that the Naimark Report did not list, cite or deposit in the HSC library archive. Thus these documents may not have been submitted to the Review. The following may therefore have been omitted from consideration because they were not made available to the Reviewer:

- (i) a contract governing the LA-03 trial issued by Dr. Spino on October 2, 1995 and co-signed by each of Drs. Olivieri and Koren later that month;⁴³
- (ii) an REB information form confirming termination by Apotex of the long-term (LA-03) trial, signed by Dr. Olivieri on July 20, 1996 and by Dr. Freedman, her division head in Hematology, on July 25, and stamped as received by the REB on August 1, 1996;⁴⁴
- (iii) a letter dated October 3, 1995 from Dr. Spino to Dr. Brittenham, copied to Drs. Olivieri and Koren;⁴⁵
- (iv) a letter dated May 8, 1996 from Dr. Spino to Dr. Olivieri, copied to Dr. Koren;⁴⁶
- (v) the full report of Apotex's Expert Advisory Panel, dated July 12-13, 1996;⁴⁷
- (vi) a letter dated July 21, 1998 from Dr. Corey to Dr. Buchwald;⁴⁸
- (vii) a chapter written by Dr. Koren in a 1993 book on research ethics which he edited;⁴⁹
- (viii) a letter dated August 12, 1996 from Dr. Spino to Dr. Olivieri, copied to Dean Aberman, Dr. Koren and Mr. Kay, the President of Apotex, Inc.;⁵⁰
- (ix) a letter dated August 13, 1996 from Dr. Spino to Dr. Agnes Klein, of Health Canada's Bureau of Pharmaceutical Assessment;⁵¹
- (x) a letter dated February 5, 1997 from Mr. Colangelo to his clients, Drs. Koren and Olivieri;⁵²
- (xi) a letter dated May 8, 1997 from Apotex counsel Mr. Brown to Mr. Colangelo;⁵³
- (xii) a letter dated July 23, 1998 from Dr. Saunders to Dr. Buchwald;⁵⁴

and pasting, and had then faxed to a Toronto newspaper reporter on October 20, 1998, together with one of his unsigned letters disparaging Dr. Olivieri. In his covering letter, HSC counsel suggested that this one page constituted the entire missing section, a suggestion which was clearly incorrect as that page was numbered, "3." Nevertheless, on January 17, 2000, HSC counsel stated, "There is nothing else to send to you." Next, on January 19, HSC counsel revised his position: "the balance of Dr. O'Brodovich's submission is a privileged document" HSC counsel claimed privilege despite the fact that the document had been addressed to, and relied on by the Naimark Review. Despite repeated subsequent requests by counsel for Dr. Olivieri, the missing pages of Dr. O'Brodovich's memo have not yet been made available to her.

(xiii) a memo dated September 5, 1998 from Dr. Olivieri *et al.* to Provost Sedra of the University and to HSC Board members;⁵⁵

(xiv) Apotex correspondence with regulatory agencies on and after May 24, 1996, including letters to Health Canada by Dr. Spino on January 28, 1997 and by Mr. Woolcock on February 25, 1997, and documents pertaining to L1 licencing submissions to regulatory agencies, January 1998;⁵⁶

(xv) a letter dated October 28, 1996 from Dr. Olivieri to Dr. Koren (copied to Dean Aberman).⁵⁷

(xvi) relevant documents from the MRC application files of Dr. Olivieri and Dr. Koren.⁵⁸

We next outline the relevance of these missing documents.

(i) The October 1995 contract is a pivotal document: it “supplant[ed]” any previous contract covering the LA-03 trial, and it gave Apotex the unilateral right “to terminate the LA-03 study” at any time. Apotex terminated this study on May 24, 1996, together with the randomized study (LA-01). The LA-03 trial cohort was precisely the patient cohort in which loss of efficacy of the drug was observed, the finding that resulted in the termination of *both* Toronto trials and the legal warnings to Dr. Olivieri not to disclose. This contract in fact had *no* confidentiality clause.

(ii) The REB form signed by Dr. Olivieri and Dr. Freedman, on July 20 and 25, 1996, respectively, officially notified the REB that Apotex had terminated the LA-03 trial, on May 24, 1996. The REB received this notice on August 1, 1996. The absence of this document from the Naimark Report’s record may help to explain why Naimark Review believed Dr. Moore, who was the REB Chair when this termination notice was received and who later stated incorrectly that the LA-03 trial continued.

(iii) In this October 3, 1995 letter, Dr. Spino re-confirmed that Apotex lacked expertise on the problem of iron-loading and asked Dr. Brittenham for assistance in identifying factors that might be involved in the apparent loss of sustained efficacy of L1 in some patients, “you have both the expertise in iron disposition and the data to help us.”

(iv) In this May 8, 1996 letter, Dr. Spino indicated that Apotex was still prepared to renew the LA-01 trial contract. This was just prior to submission of the revised patient information and consent forms to the REB by Dr. Olivieri, which was immediately followed by the abrupt termination of the trials and legal warnings to Dr. Olivieri.

(v) In letters dated August 23, 1996 and September 18, 1996 to Dr. Moore, Dr. Olivieri conveyed a copy of her “Review and Commentary” on the report of the Apotex Expert Advisory Panel (EAP) on data from the terminated trials. These letters were sent to Dr. Moore because Apotex had only provided

“excerpts” from the EAP report to Dr. Moore, with a letter from Dr. Spino on July 29, 1996,⁵⁹ and Dr. Olivieri suggested Dr. Moore should have seen the full EAP report and compared it with her “Review and Commentary.” The Naimark Review (at page 36) quotes from these excerpts, but the complete EAP report is not referenced in the Naimark index or archive. The full EAP report is important because, through it, Apotex bolstered its position that there was a “scientific disagreement,” rather than an issue of ethics that arose because the industrial sponsor attempted to prevent the principal investigator from disclosing a risk. The EAP report is important also because it stated that both trials were terminated, “It is unfortunate that these studies [LA-01 and LA-03] were *stopped* prematurely....”⁶⁰ (emphasis added)

(vi) The July 21, 1998 letter from Dr. Corey, a member of the EAP, advised Dr. Buchwald that “the expert panel set up by Apotex may not have had all the information necessary to form unbiased conclusions.”

(vii) In 1993 Dr. Koren, who had served as Chair of the Hospital’s REB, had written a book chapter stating that among “studies which do not need approval of HSRC (later termed the REB) in Toronto” are: “Retrospective chart reviews;” and “Compassionate use of an experimental drug.”⁶¹ The latter is another term for Health Canada’s Emergency Drug Release program, under which the supply of L1 was reinstated after termination of the two trials. This information confirms that, under HSC policy, Dr. Olivieri was not required to obtain REB approval to treat patients under EDR, and that she was not required to obtain REB approval to publish data obtained from chart review.

(viii) In his August 12, 1996 letter, Dr. Spino issued another warning to Dr. Olivieri that “Apotex would take appropriate action” if any information released by Dr. Olivieri affected “the commercial viability of this product (L1).” The specific purpose of this letter was to deter Dr. Olivieri from presenting her findings on L1 at the upcoming meeting of the American Society of Hematology, a direct infringement of her academic freedom, and against the public interest.

(ix) Apotex’s August 13, 1996 letter to the Health Protection Branch addressed Dr. Olivieri’s planned meeting the next day with the regulator agency to disclose the risk of loss of sustained efficacy of L1. This letter, taken together with a letter dated August 14, 1996 from Apotex counsel Ms. Kay to Dr. Olivieri’s counsel Mr. Colangelo (that was listed in the index in the Naimark Report),⁶² contradicts a finding in the Naimark Report—that this meeting was held “in accordance with the agreement in the June [1996] mediation meeting convened by Dean Aberman.”⁶³ In fact, these two letters document Apotex’s opposition to Dr. Olivieri’s meeting with HPB: the

August 13 letter said a meeting of Dr. Olivieri with HPB would serve “no useful purpose;” and the August 14 letter said this meeting was “inappropriate” and that “Apotex is prepared to take whatever legal steps are necessary in order to ensure that the conduct [of Dr. Olivieri in moving to disclose the risk] ceases and to obtain appropriate compensation for damages sustained.”

Also in this letter, Apotex advised HPB that Dr. Koren had supported its position on L1 since February 1996 and “disagreed with Dr. Olivieri’s interpretation of the data.” Several times during 1996, Dr. Koren made statements to Dr. Olivieri (including those he made in an August 1996 meeting with their joint CMPA legal counsel), and co-signed letters with Dr. Olivieri, that he supported her view, not Apotex’s. (See sections 5F and 5H.)

(x) The February 5, 1997 letter of CMPA counsel to Drs. Olivieri and Koren conveyed to Dr. Koren the detailed report on the risk of progression of liver fibrosis Drs. Olivieri, Brittenham and Cameron had drafted for the regulatory agencies. The finding that L1 had caused progression of liver fibrosis in some patients had been made only a few days earlier, and Dr. Koren confirmed in late 1999 that he had received the copy of the report sent to him through Mr. Colangelo very shortly after it was sent. (See section 5K.) Not having this letter, the Naimark Report concluded incorrectly that Dr. Olivieri had not provided information on this risk to Dr. Koren.⁶⁴

(xi) The May 8, 1997 letter of counsel for Apotex confirmed to counsel for Dr. Olivieri that Dr. Spino would be meeting with a group of Dr. Olivieri’s patients that day. This meeting was convened without Dr. Olivieri’s approval. During it, Dr. Spino told the patients that L1 was as effective as the standard treatment, deferoxamine and, rather than cause progression of liver fibrosis, L1 could prevent it. He also told the patients that L1 would soon be licenced in Italy (the main sites for the LA-02 trial were in Italy).⁶⁵

(xii) In his July 23, 1998 letter Dr. Saunders informed Dr. Buchwald that he had recently signed a contract with another drug company which was at least as restrictive on communication of information as the one Dr. Olivieri had signed in 1993, yet this contract had been formally reviewed and approved by the Hospital administration. The Naimark Review might have made stronger recommendations about policy on research contracts and its implementation by HSC had it been aware of this.

(xiii) The September 5, 1998 memo of Dr. Olivieri *et al.* laid out their responses to claims the Hospital Executive had made in an e-mail letter to many scientists and physicians in the Hospital and the University on September 1. It includes important information not addressed by the Naimark Report. For instance, Dr. Olivieri documented that she met with patients on February 4, 1997 to advise them of the risk of progression of liver fibrosis, immediately

after Dr. Cameron had confirmed it, thus fulfilling her ethical obligation. The Naimark Report implied that she not fulfilled this obligation.

This memo reported that Dr. Spino had attended Dr. Olivieri's presentation at the December 1996 ASH meeting, and that he had publicly stated in the meeting that her co-investigator in Toronto (i.e., Dr. Koren) did not agree with her findings on L1. In this memo Dr. Olivieri also questioned the late arising allegation by Apotex that it had terminated the trials because of protocol violations, noting that Apotex itself had stated in 1996 and 1997 that the reason it terminated the trials was in an effort to prevent Dr. Olivieri from informing patients of a risk.

(xiv) The letters by Dr. Spino and Mr. Woolcock of Apotex to Health Canada in early 1997 confirmed that Apotex had stopped both the LA-01 and LA-03 trials in May 1996. The Naimark Report (page 135) erroneously concluded that the trials were stopped in May 1997.

Documents pertaining to Apotex's January 1998 licencing applications for L1 show that Apotex was now downgrading the significance of the Toronto trials (LA-01 and LA-03), and elevating the significance of the short-term safety trial at international sites (LA-02) by re-casting this as the "pivotal" trial for licencing. Apotex also now alleged that "the investigator" (Dr. Olivieri) had committed protocol violations which compromised the data from the Toronto trials. It further now alleged that "protocol violations" were the primary reason it terminated these trials. These documents show that Apotex had an interest in and was actively seeking to discredit Dr. Olivieri.

(xv) In her October 28, 1996 letter to Dr. Koren, copied to Dean Aberman, Dr. Olivieri raised concerns about Apotex's second interruption in the supply of L1 and reported a possible reason for it. She noted that the patients were concerned and that Apotex was not living up to the agreement mediated by Dean Aberman whereby Apotex undertook to reinstate the supply under EDR. In this letter she repeated the information she had already given to the REB in July that both trials (LA-01 and LA-03) were terminated and the patients on L1 were no longer enrolled in any trial. Had the Naimark Review been provided with this letter, it might have come to a more accurate understanding of important issues and events.

(xvi) On June 25, 1992, MRC advised Dr. Olivieri that it would not (by itself) continue to sponsor her L1 studies (commenced with MRC support in 1989) beyond the next year, and awarded her a "terminal grant" for 1992-1993. In 1993 she re-applied to MRC under its university-industry program, for funding for a new randomized trial of L1, following agreement by Apotex to be the industrial co-sponsor. On September 27, 1993, MRC awarded Dr. Olivieri a

three-year grant for the new randomized trial. This application to MRC included trial specifications that were more elaborate than those of the 1989–1993 pilot study, and specified a much larger cohort of sixty-six trial participants. The randomized trial (called LA-01) was a different trial from the ongoing pilot study (that continued as LA-03) with Apotex supplying L1 for both trials. This is significant because Dr. Moore said incorrectly that some patients who had been in the LA-01 trial continued after its termination in the LA-03 trial which, according to her, continued. In fact both trials were terminated. Even if LA-03 had not been terminated, Dr. Moore did not explain how patients from the LA-01 cohort could be placed in a “trial” that had a quite different protocol, including different enrolment criteria. (See section 5A for citations.)

It is also relevant that the applications to MRC identified Dr. Olivieri and Dr. Koren as professors in the University of Toronto, and the applications were endorsed by the University, as well as the Hospital. Indeed under the university-industry program, the applicants were required to specify their university affiliation and to have the application approved by a representative of their university. (See sections 5.O.2(4) and 5.N(8).)

The omission of all these relevant documents from the Review’s record of documentation provided to it is surprising. The non-participation of Dr. Olivieri in the review cannot account for the omission. The review was supplied with voluminous correspondence and other documentation involving Drs. Spino, Koren and Olivieri, by Dr. Spino and by Hospital and University administrators. Persons listed among Review participants had one or more of the sixteen documents listed above. We do not know with certainty whether or not Dr. Naimark received any these sixteen documents because, as noted earlier, some documents he did receive were neither listed in the appendix nor deposited in the HSC library archives. However, if the Naimark Review was not given these documents, it would help to explain the positions the Review took with regard to the issues to which these documents relate. Given that the number of these relevant documents is sufficiently large that it would be hard to overlook all of them, it is likely that the Review was not provided with some or all of these documents. In such a circumstance of incomplete information provision, an inquiry may reach incorrect conclusions and did so in this case.

(5) Incorrect information

The Review’s task was made even more difficult—not only was the documentation given to it incomplete, but it was provided with incorrect information. It is now clear that information the Review relied on is incorrect in fundamental respects. The incorrect information was submitted primarily by

Dr. Koren, Dr. O’Brodivich, Dr. Moore and Dr. Spino (see section 5.O.2). The narrative outlined in the Naimark Report reflects the outline of events constructed by Dr. O’Brodivich (in his lengthy memo of September 24, 1998), with supporting information from Drs. Koren, Spino and Moore. Inclusion of the documents listed above in Dr. Naimark’s information base could have led to identification of the inaccuracies in this narrative.

A year after the Naimark Review, it was established through Dr. Koren’s own admission of responsibility that he had sent anonymous letters against Dr. Olivieri and her supporters, and had persistently lied to cover this up (see section 5R). These anonymous attempts to discredit Dr. Olivieri began during the period Dr. Koren was also submitting information against Dr. Olivieri to the Naimark Review, both directly and through Dr. O’Brodivich (see section 5.O.2).

(6) Conclusions

1 | In response to widening controversy and numerous calls for an independent inquiry, the Board of Trustees of the Hospital for Sick Children decided to appoint Dr. Arnold Naimark to review the L1 dispute and give them a written report. The Naimark Review was controversial from the outset in that it was constituted with the concurrence of only one of the parties to the dispute. A reasonable, widely recognized condition—reviewer selection by both parties—could have resulted in the participation in the Review by Dr. Olivieri and her supporters, but was not met. The two associate reviewers picked by Dr. Naimark were not involved until late in the process.

2 | The documentary basis for the findings of the Review was seriously compromised by relevant documents apparently not being made available, and by incorrect information in some documents that were made available.

3 | We have seen no explanation as to why some documents relied on by the Naimark Report were not deposited in the HSC library archive. However, a number of such documents were made available to this Committee of Inquiry by other sources, and this was of value to us in assessing the Report.

4 | The appointment of Dr. Naimark was announced on September 9, 1998 and he was asked to report to the Board by November 30, 1998.⁶⁶ His Report was made public by the Hospital on December 9, 1998. In view of the complexity of the case, the relatively short time allotted for it may have been

an additional disadvantage, since inconsistencies in its documentary base were not pursued and resolved in the Report (see section 5.O.2).

5.O.2. The Naimark Report

(1) Overview

THE HSC BOARD OF TRUSTEES characterized the Naimark Report as “thorough and reliable,”⁶⁷ and “fair.”⁶⁸ It was used by the Hospital and by Apotex as a basis of actions against Dr. Olivieri,⁶⁹ and by the University of Toronto as a basis for suggesting it had protected Dr. Olivieri’s academic freedom.⁷⁰ Therefore, it is important to assess any limitations to the validity of the report.

Together with the facts and circumstances of the L1 clinical trials, the 150-page Report discusses policy. Its policy analysis is substantial and contains many valuable comments and recommendations. However, because the Review apparently lacked access to some relevant documents and was given incorrect information by some “primary submitters,” it contains serious errors of fact and interpretation regarding events and circumstances. Some errors might have been avoided if the Reviewer and his associate reviewers had used a high index of suspicion. Had they pursued certain inconsistencies in information, or been more stringent in examining the documentation, they might have been led to different conclusions, but they did not have the benefit of the more extensive documentation the present Inquiry has, or the benefit of a knowledge of the dishonesty of a central figure, Dr. Koren, whose honesty they had no *a priori* reason to doubt. Our index of suspicion alerted us to question with rigour many details we might otherwise not have noticed. We conclude that the Naimark Report does not provide a complete or accurate representation of the L1 trials and post-trial events. In particular, its finding that Dr. Olivieri had failed in a reporting obligation is wrong.

(2) The Hospital’s “weak policy infrastructure”

The Naimark Report found that the Hospital’s policies on clinical trials and contract research were not sufficiently robust. It also found that existing policies were widely disregarded, and not enforced:

There was no policy that clearly required review and approval of contracts in advance. Some investigators did submit proposals for approval but apparently many did not.⁷¹

In regard to personal services (consulting) contracts, the report found:

[C]ompliance with reporting requirements or expectations was not monitored, and lack of compliance was apparently common.⁷²

It also noted:

The policy infrastructure in the Research Institute (of the Hospital) was weak at the time the L1 Clinical Trials were initiated. ...

At the time the Trials Contract was executed (1993), the requirement for detailed a priori institutional review of contracts with external sponsors, if

there was one, was articulated so imprecisely and, we are told, was so frequently ignored as to be, for all practical purposes non-existent.⁷³

Unfortunately, the Report did not review in comparable detail the policy environment of the Hospital's Research Ethics Board (REB) or the incorrect information submitted on REB involvement in L1 matters. This may have contributed to the Report's mistaken conclusion that Dr. Olivieri failed to report the second unexpected risk of L1 (progression of liver fibrosis) to the REB in a timely manner, when, in fact, there was no requirement either in HSC policy or practice for her to report to the REB on this matter. (See sections 5F, 5G, 5H, 5J and 5K.)

The Naimark Report made many useful recommendations for improvements in HSC policy and practice. These included strengthening of the REB policy infrastructure, establishment of a clinical trials secretariat, and examining the need for a grievance procedure for professional and scientific staff.⁷⁴

The Report's policy recommendations were considered by the Hospital and the University in subsequent reviews. The Hospital established a task force to review its research policies (the second phase of the review announced in September 1998) and the University asked Professor Bernard Dickens to lead a review on harmonization of policies between the University and its affiliated health care institutions. These reviews issued reports in 1999.⁷⁵

(3) Limitations of the Report

The Naimark Report presents an account of events and circumstances that is incorrect in some important instances. In other important instances, the Report is sufficiently incomplete or inaccurate that readers of it may come away with misunderstandings. Many of the Report's limitations and errors may be attributed to the disadvantages of not having certain relevant information, as well as having been given incorrect information. It was not alerted as we were to be rigorous in pursuing inconsistencies in the information submitted to it, or in resolving inconsistencies in its own descriptions. As a result, it did not investigate and address several important questions. It also used language in a way that obscured important issues. We provide representative examples in the following paragraphs.

I. CONTRADICTORY INFORMATION PUT FORWARD BY DR. KOREN

On February 4, 1997, immediately after Dr. Olivieri identified a second unexpected risk of L1 (progression of liver fibrosis), she informed patients and Apotex, and one day later (February 5) she also informed Dr. Koren. Both Apotex and Dr. Koren were provided with the full report she planned

to send to regulatory agencies, though her CMPA counsel.⁷⁶ Dr. Koren later submitted a letter to the Naimark Review that was signed by him and addressed to Dr. Olivieri, that he said he had sent to her and which bore the date, “Feb 8, 1997.” The opening sentence said:

I was shocked and dismayed to receive [sic] your analysis of liver toxicity of L1.

This letter was reproduced in full in the body of the Naimark Report, at page 41, an indication that it was given weight. However, at page 134, the Report said:

No information was provided by Dr. Olivieri to... Dr. Koren... about this serious adverse reaction until inquiries were made of her in the latter part of February 1997.

By the latter part of February, the Report meant February 19, 1997, as it makes clear on page 42. Thus, Dr. Koren had stated in writing, in a letter the Naimark Report reproduced in full, that he had received Dr. Olivieri’s report by February 8. Yet the Report simultaneously accepted his information that he had received no information from Dr. Olivieri on this matter until February 19. This discrepancy in dates is significant and important, for the following reasons. First, one of the accounts Dr. Koren gave to the Review must be false. If the Naimark Review had investigated this discrepancy, it might have been led to different conclusions on important issues. The correct information is that Dr. Koren received Dr. Olivieri’s report on the newly identified risk on or before February 8, 1997, since the Humphrey Report stated:

Dr. Koren acknowledged that he had received a copy of the letter from Dr. Olivieri’s [CMPA] counsel at McCarthy Tétraut in early February 1997, together with a bound book of documents relevant to the liver toxicity issue.⁷⁷ *

Second, according to his own “February 8” letter that was reproduced in the Report, as well as his admission to Ms. Humphrey, Dr. Koren knew of the risk of progression of liver fibrosis by that date. This is significant because, as we discuss below, the Report incorrectly found that Apotex had only terminated its “sponsorship” of the L1 trials in Toronto, and that the trials “continued,” so that the patients were still subjects of research under a protocol that specified both Dr. Olivieri and Dr. Koren as investigators. Although in fact this was not the case, the Review panel members found as a consequence of this incorrect interpretation that Dr. Olivieri had an obligation to report the risk to the REB in a timely manner, since they thought

*The Naimark Report stated (at page 42) that Dr. Koren received a copy of Dr. Olivieri’s report from Apotex. If so, this would have been additional to the copy Dr. Olivieri sent him through their joint legal counsel on February 5, 1997. The source of the information was irrelevant to the obligation to report it that Dr. Koren said he had.

there was still an ongoing trial. Since Dr. Koren was also an investigator, by the Report's own logic Dr. Koren should have had the same obligation as Dr. Olivieri to report the risk to the REB. Therefore, the Report should have concluded that he too had failed to fulfil it. Indeed, in another letter Dr. Koren submitted to the Review, purportedly sent on "December 18, 1996," he stated that he had been informed that she had information on "L1 liver toxicity," and further that it was *he* who had the obligation to "report on any ADR (Adverse Drug Reaction)." The Naimark Report also produced this letter in full at page 41.⁷⁸ Yet the Report did not make the same finding of failure to notify the REB against Dr. Koren, as it did against Dr. Olivieri. It did not explain why.

The Naimark Review in fact had independent documentary evidence that Dr. Koren had the full information on the new risk, but had not reported it until he was asked about it by Dr. O'Brodovich. Dr. O'Brodovich wrote to Dr. Olivieri's CMPA counsel Mr. Colangelo on March 3, 1997:

...[O]n Wednesday morning, February 19, 1997 I contacted Dr. Koren who informed me that Apotex had recently forwarded to him... the package of information which you had apparently sent, on behalf of Dr. Olivieri, to Apotex.⁷⁹

Dr. O'Brodovich acted against Dr. Olivieri in February 1997 (see section 5K) and during the Naimark Review, but did not act against Dr. Koren even though (following his own logic) both Dr. Olivieri and Dr. Koren had committed the same alleged "failure." This fact also went unremarked by the Review.*

*There are other contradictions and inconsistencies pertaining to Dr. Koren's purported letters of "February 8, 1997" and "December 18, 1996." These are discussed later, in subsection 5.O.2(6).

II. APOTEX TERMINATED THE TRIALS, NOT MERELY ITS SPONSORSHIP

The question of whether or not Dr. Olivieri *had* an obligation to report adverse findings (risks) to the Research Ethics Board, after the trials were terminated, was not investigated and addressed in the Report. The Report's discussion (pages 41–48) assumes that she had this obligation, apparently on the basis of a belief that those patients who continued on L1 after May 1996 were still enrolled in a trial. At page 44, the Report cites letters Dr. O'Brodovich and Dr. Moore wrote on February 20, 1997 (to Dr. Baker and Dr. Olivieri, respectively) indicating that they were conducting themselves as if this were the case. However, the Report cites no primary HSC or other documents to substantiate the views of Drs. O'Brodovich and Moore. In fact, the Report's documentary base included clear and abundant evidence originating with Dr. Spino of Apotex, Dean Aberman, Dr. Koren, Dr. Olivieri and others confirming that both trials were terminated and no trial was continued (see below). However, the Report did not address the central fact that the views of Drs. O'Brodovich and Moore were contradicted by these primary documents. It appears that the Naimark Review panel relied on the views of Dr. Moore and Dr. O'Brodovich in reaching its incorrect conclusions that patients continued in a trial after the terminations, and consequently remained under REB jurisdiction, despite the contradiction in the documents available to the Review.

In his memo of September 24, 1998 to Dr. Naimark, Dr. O'Brodovich asserted that Dr. Olivieri had an obligation to report to the REB after Apotex terminated the trials. The only evidence given in support of his position is a letter received from Dr. Moore on June 3, 1998 saying, "confirmation that withdrawal of funding by Apotex 'does not negate or terminate REB approval.'"⁸⁰ (The inner quotation is from Dr. Moore's letter.) Dr. Moore was simply wrong: Apotex not only terminated its funding (sponsorship) for the LA-01 and LA-03 trials in Toronto, it terminated the actual trials.*

The Naimark Report contains serious errors and unresolved inconsistencies on this matter. It states that Apotex terminated both trials in some places, yet in others frames the terminations incorrectly as "Non-renewal of Apotex sponsorship."⁸¹ The latter reflects the incorrect information put forward by Dr. Moore and Dr. O'Brodovich. The Review had copies of Apotex's letters to Dr. Olivieri and Dr. Koren, and to senior Hospital administrators, stating that it had terminated the trials, and cited some of these letters. For instance, it had copies of the original termination letter of May 24, 1996 from Dr. Spino to Drs. Olivieri and Koren, Dr. Spino's letter to Dr. O'Brodovich of May 22, 1998, and Dr. Spino's letter to HSC President

*The documentary evidence showing that Dr. Moore was wrong is discussed in sections 5F, 5G, 5H and 5K.

Mr. Strofolino of August 31, 1998. Citing the May 24, 1996 Apotex letter, the Naimark Report says, “the LA-01 and LA-03 trials were being discontinued at the HSC and the Toronto Hospital.”⁸² It also quotes from Dean Aberman’s account of his June 7, 1996 mediation meeting: “Apotex would not change their position on discontinuing the clinical trials.”⁸³ Despite these unequivocal statements that termination meant termination and nothing less, the Report goes on to discuss “Consequences of Non-Renewal of Apotex Sponsorship,” and events after “Apotex terminated support for the trials.”⁸⁴ A consequence of this usage is that inconsistencies in the Review’s evidentiary base and in its own account of events were obscured.

There are repeated references to “the Trials [plural] Contract,”⁸⁵ which suggests that the April 1993 LA-01 contract was the only executed contract for the Toronto trials, and that it somehow governed the LA-03 trial as well. This error is understandable if we infer (from the absence of reference to it) that the Review panel was not given a copy and had no knowledge of the LA-03 contract executed in October 1995. As noted in section 5.O.1, the panel also appears not to have seen the written notification of termination of the LA-03 study that the REB received from Dr. Olivieri on August 1, 1996. Had the panel members seen these two documents, they would have realized that Dr. Moore was wrong: the LA-03 trial was in fact terminated on May 24, 1996.

Another source of possible confusion lay in the varied and occasionally inaccurate terminology used by the clinical investigators and their assistants. The long-term trial was variously called “the pilot study,” or “the compassionate use trial,”* the latter because it was a non-randomized trial involving patients unwilling or unable to accept the onerous standard therapy. It came to be termed “LA-03” only after 1993, when Apotex agreed to supply L1 for this trial free of charge. There was an understandable delay before the new term LA-03 was in uniform usage. In the same fashion, the April 1993 contract for the new randomized trial that came to be referred to as LA-01, nowhere contains the term “LA-01.” Only later were the randomized trial and its corresponding April 1993 contract regularly referred to in documents as “LA-01.” Another significant instance of a delay in converting terminology appears in the protocol for the short-term safety trial at international sites (LA-02. The LA-02 protocol as modified on July 21, 1995 still listed Drs. Olivieri and Brittenham as “investi-

*The term “compassionate use” can refer either to a trial situation, or a non-trial situation. At HSC there was no requirement for REB approval, unless there was an active trial protocol. In the EDR arrangement for supply of L1 after the trials were terminated, there was no active protocol and so REB approval was not required. This new arrangement was sometimes also referred to as “compassionate use.”

gators,” as they had originally been designated in 1994, even though by 1995 they were consultants not investigators (see section 5B).⁸⁶

Similarly, after both Toronto trials were terminated, and some patients reinstated on L1 treatment under EDR, the two groups of patients continuing to receive the drug (subgroups of the former trial cohorts) were for shorthand still casually referred to as being in “trials” or “studies,” although in fact they were not. An example of this usage occurs in the letter Drs. Olivieri and Koren sent the former REB Chair Dr. Zlotkin (copied to the new Chair Dr. Moore), on July 15, 1996. They said, “APOTEX abruptly terminated these [LA-01 and LA-03] studies,” and explained the basis on which L1 treatment would be continued for some patients in the post-trial EDR arrangement. In this context, they added, “we do not intend to enroll additional patients on this trial” (in regard to the former LA-03 cohort), and “no further patients will be randomized [enrolled]” (in regard to the former LA-01 cohort).⁸⁷ Taken out of context, these quotations could lead to confusion. Possibly they did confuse the Naimark Review panel members, who reported, “In mid-July 1996, Drs. Olivieri and Koren wrote to Dr. Zlotkin describing their proposed course of action with respect to patients enrolled in the LA-01 and LA-03 trials following the discontinuation of sponsorship by Apotex.”⁸⁸

Notwithstanding their use of confusing terminology, that Dr. Olivieri and Dr. Koren were not confused can be seen from the full context of their July 15, 1996 letter and other documentation from the time. Dr. Olivieri clearly understood that both trials had been terminated, and formally reported this to the REB in the information forms she and Hematology Chief Dr. Freedman sent to the REB later in July, forms the REB received on August 1. These state that both the LA-01 and LA-03 trials had been terminated on May 24, 1996. However, it appears that the Naimark Review received a copy of only one of these formal notifications—for LA-01. In the letter Dr. Olivieri sent to Dr. Koren and copied to Dean Aberman on October 28, 1996, expressing concerns over the second stoppage in the supply of L1 by Apotex, she noted that the patients were no longer “enrolled” in trials, but had continued on L1 under the EDR arrangement mediated by Dean Aberman. The Review appears not to have had a copy of this letter either.

It is relevant to note, however, that the Naimark Review did have copies of additional documents confirming that both trials had been terminated in May 1996. For instance, it had copies of five letters written by Dr. Koren in 1997 and 1998 in which he referred to the terminations of LA-01 and of LA-03.⁸⁹ It also had a copy of a letter the administrator for contracts and grants in the HSC Research Institute, Ms. Anne Marie Christian, to Apotex’s Chief Financial Officer in which she stated:

I have your letter about the clinical trials LA-01 and LA-03 which were terminated.⁹⁰

Thus the Naimark Review panel's belief that a trial (or trials) continued after May 1996 is not borne out by clear and unequivocal documents available to it.

III. INADEQUATE INVESTIGATION

Continuation of funding for Dr. Koren's research after termination of the trials. After the trials were terminated, Apotex continued to provide support for Dr. Koren's research programs through salary support for research fellows under Dr. Koren's supervision. They continued work on the close-out of the terminated trials, and thereafter on data from the trials. The Naimark Report says that after May 1996 Dr. Koren did not conduct "studies independently of Dr. Olivieri pertaining to the safety of L1 in patients."⁹¹ It is true that Dr. Koren did not undertake new independent clinical studies of L1 in thalassemia after May 1996, but this does not mean that he was not doing research on L1.

In fact, Dr. Koren and his Apotex-funded research fellows were co-authors of the two abstracts on LA-01 and LA-03 data favourable to the drug, that Apotex employee Dr. Fernando Tricta presented at the April 1997 conference in Malta. In 1998 Dr. Koren and two of the fellows wrote an article on the efficacy of L1* in thalassemia which used data from the terminated LA-03 trial. The Naimark Review had documentation on these publications. For instance, on the article written in 1998, the following documents were submitted to the Review: a copy of Dr. Koren's handwritten notes of a meeting with Apotex staff in May 1998 in which the contents of the article were discussed; a copy of the article submitted to the journal *Therapeutic Drug Monitoring* in the summer of 1998; and the journal editor's letter of October 1998 accepting the article for publication.⁹² It was published in 1999 (see section 5R.)

It is hard to understand why the Naimark Report did not comment in depth on this post-trial research work using existing data on L1 in thalassemia, because an aspect of the L1 controversy publicized in August 1998 was the allegation that Dr. Koren had received very substantial research funding from Apotex, and had published results favourable to Apotex's position on L1 that were relied on by the company. The Naimark Review had a copy of Dr. Koren's letter to HSC Board Chair Mr. Pitblado dated August

*Aside from issues of drug toxicity, efficacy of an iron-chelation drug is itself a matter of safety because ineffective chelation exposes thalassemia patients to the chronic toxicity of iron loading that results from their transfusion dependence.

20, 1998 in which he referred to media coverage of this allegation he considered to be “untrue and defamatory.”⁹³ By saying only that Dr. Koren had done no clinical “studies” after “Apotex terminated support for the trials,”⁹⁴ the Report obscured the facts that: (i) he had continued analysis and publication on L1 in thalassemia after the trials were terminated; (ii) he had received post-trial financial support from Apotex for this work; (iii) he had discussed the results with Apotex prior to submitting an article on this work to the journal; and (iv) he had not disclosed Apotex financial support in the article.

The second stoppage by Apotex of the L1 supply. The Naimark Report suggested that this second stoppage in the drug supply in the fall of 1996 was due to difficult relations between Dr. Olivieri and Dr. Spino, and concluded that documentation on this interruption was “not critical to the main issues.”⁹⁵ Strained relations may indeed have been a factor, but this does not explain why Apotex still did not promptly reinstate the supply after Dean Aberman had again arranged for Dr. Koren, who had good relations with Dr. Spino, to act as intermediary in the supply, as had been arranged in June 1996. Here again the Naimark Review may have been disadvantaged by not having full information. A document from the time suggests another possible reason, and had the Review been in possession of a copy, it might have stimulated to further questions. This is a letter dated October 28, 1996 which Dr. Olivieri wrote to Dr. Koren (copied to Dean Aberman), noting that one of her assistants, who was in contact with Apotex, had said that the company had concerns that she would “analyze and report this data [results of monitoring patients on L1 under EDR], even if unfavourable.”⁹⁶ We discuss this matter in section 5J(3), but note here that Dr. Olivieri was under legal and ethical obligations to monitor the patients under EDR, and to report the results of monitoring to Health Canada, a fact that *was* critical to the main issues. Furthermore, Apotex acted without due concern for the interests of patients, but Naimark Report did not address the question of Apotex’s conduct.

Inaccurate assessments regarding contracts with publication restrictions. The Naimark Report suggested that the one-year, post-termination publication ban in the LA-01 contract did not conform to existing policy. This was not the case: this clause did not violate existing policy, indeed such clauses were expressly permitted under University of Toronto policy.⁹⁷ The Report suggested also that Dr. Olivieri was remiss in not having the contract formally reviewed by the Hospital administration. We agree on this. However, the following statement in the Report is misleading:

The Hospital had no knowledge of the Trials Contract before its execution and therefore was not in a position to deter the investigators from incurring inappropriate restrictions on the release of information.⁹⁸

This suggests the Hospital might have refused to approve the contract had it been asked to review the provisions in advance. Documentary evidence shows that the Hospital administration is unlikely to have deterred the investigators from signing this contract. It is probable that the administration would have approved the contract, because at least one other similarly restrictive contract, between Dr. Fred Saunders, a program director in the Division of Haematology/Oncology, and another drug company was formally approved (see section 5.L(4)). It appears that the Naimark Review did not ask the Hospital for copies of other research contracts signed with drug companies during the years 1993–1998 for comparison, to see what the practice in the Hospital actually was. It also appears that the HSC administration did not voluntarily provide such information.

The dispute between Dr. Olivieri and Apotex arose from data on patients who had been in the long-term (LA-03) trial, and the contract for it had *no* publication ban. It is hard to understand why the Naimark Review apparently was not provided with a copy of this highly relevant document—the LA-03 contract.

The LA-02 trial and the consulting contract. The Naimark Report says:

Apotex, faced with escalating costs and a small and uneconomic market potential in Canada, was urged by Dr. Olivieri and Dr. Garry [sic] Brittenham to complement the Canadian studies with a large international trial.⁹⁹

A brief summary of the facts of the matter is necessary in order to assess whether this statement is accurate. The American Food and Drug Administration (FDA) had said that a short-term acute toxicity trial (safety trial) would be necessary before it would consider granting a marketing licence for L1. Apotex agreed to sponsor this trial because it intended to apply for a licence to market L1 in the USA.¹⁰⁰ Thus, in 1994 Apotex “initiated plans... including the submission of an IND [Investigational New Drug] application to the FDA for approval.”¹⁰¹ The short-term safety trial was termed LA-02. Any “urging” by Drs. Olivieri and Brittenham would have been much less persuasive than the fact the FDA required such a trial. (See section 5B.)

All parties were well aware from the outset that the number of thalassemia patients in Canada was small, the largest concentration being in the Toronto area because of immigration patterns of recent decades. The known acute toxicity affects of L1, severe loss of white blood cells due to bone marrow suppression and joint damage, had been observed in only a few patients. A trial to assess this risk would therefore require a much larger cohort of patients than was available in Canada.

IV. USE OF LANGUAGE THAT OBSCURED ISSUES

Two examples of the Report's usage were noted above: the phrase "non-renewal of Apotex sponsorship of trials," to describe what was actually *termination* of the trials by Apotex; and the statement that Dr. Koren conducted no "studies" after May 1996, which obscures the fact that he did further research and analysis on data from the L1 trials and published it. There are other examples.

i) The Report says that University and Hospital officials made representations "behind the scenes"¹⁰² to Apotex concerning its legal warnings to Dr. Olivieri:

These personal representations were private interventions which, because they were apparently unknown to Dr. Olivieri and others, could not reassure concerned members of the staff that Dr. Olivieri had the Hospital's moral support on matters of principle that were of concern to her and others. The absence of manifest moral support contributed significantly to the intensity and spread of the controversy.¹⁰³

This was not the issue. A number of scientists from HSC and elsewhere had contacted University and Hospital officials in 1997 and 1998 to express concerns over lack of support for Dr. Olivieri, and were invariably told that any problems of institutional interest had been solved and that she herself had been adequately supported. The Naimark Review had copies of much of the relevant correspondence (see sections 5L and 5N). Dr. Olivieri and others knew that there had been "private interventions," because the scientists who contacted University and Hospital officials reported the responses to her.* The issue was that the private interventions were not effective and the full authority of neither institution was brought to bear to make them effective. The concerned scientists urged effective interventions. Later, when there was still no evidence that any such interventions would be forthcoming, many scientists asked for an independent inquiry into the matter. Both the Hospital and the University have relied on the Naimark Report as providing proof that they had provided effective assistance to Dr. Olivieri.¹⁰⁴

ii) The central matter of the dispute was a question of ethics. A clinical researcher finding an unexpected risk in a clinical trial has an obligation to inform patients, but a commercial enterprise attempted to prevent this. It is not relevant whether the risk is eventually validated by independent studies—the risk may or may not turn out to be real. But once a clinical investigator judges

*For instance, Dr. Robert Phillips spoke with Dean Aberman on July 2, 1997. He reported to Dr. Olivieri in an e-mail immediately thereafter that Dean Aberman had said, "he has made many efforts to help you with Apotex." A letter Dr. Phillips wrote to Dean Aberman on September 22, 1997 indicates that he did not consider the Dean's efforts were adequate or effective. In a reply on October 1, 1997, Dean Aberman disagreed with Dr. Phillips.

there is a risk to patients, he or she has an ethical duty to inform them. Only then can patients decide if they want to participate further and take the risk. However, senior administrators of the Hospital and the University framed the issue as a “scientific disagreement,”¹⁰⁵ rather than a matter of ethics, and the Naimark Review accepted this view. In support of this interpretation the Review presented a very broad definition of “scientific disagreement,” that included any disagreement on a scientific question between any scientists, whether or not they had relevant expertise.¹⁰⁶ This meant important aspects of the controversy were then not addressed: the possible adverse impact of the abrupt termination of the trials on the health and interests of patients who had volunteered to be trial subjects; and infringement of the right to academic freedom of a clinical researcher, Dr. Olivieri.

A clinician treating patients in a non-trial setting, such as the post-trial EDR arrangement in this case, has a corresponding ethical obligation to inform patients and others with a need to know of any unexpected risk of treatment that may be identified. This was the situation in February 1997 when Dr. Olivieri identified the second risk of L1. In this circumstance also, Apotex tried to impede communication about the risk by using legal warnings and relying on purported scientific disagreement. The Naimark Report did not adequately investigate and address the central issues of research and clinical ethics, possibly because it accepted Apotex’s claims that it had not attempted to impede Dr. Olivieri from communicating about risks. It may have been disadvantaged by having copies of only some of the legal warning letters sent by Apotex. (See sections 5I and 5.O.2(7).)

iii) The Report says, “Dr. Olivieri had continuing and frequent access to competent legal counsel.”¹⁰⁷ The competence of her CMPA counsel was never at issue. The issue here is that the CMPA counsel represented her as an individual client facing warnings of legal action and their approach was one of minimizing a client’s legal exposure. It is not the responsibility of the CMPA to defend either academic freedom or principles of research ethics—these are the responsibilities of universities and their affiliated teaching hospitals. The institutions and their legal counsel should have been involved in defending these principles.

iv) The report says, “The principal investigators and their associates were eminently qualified both clinically and scientifically to conduct the trials.”¹⁰⁸ We agree that the Toronto iron-chelation research group (see section 5A(2)) was eminently qualified as a group. This statement in the Report could be read to mean that Dr. Koren had the medical expertise and training to differ from Dr. Olivieri in assessing risks of treatment in patients with thalassemia major, when in fact he did not.

(4) Institutional responsibilities and interests

We agree with the Naimark Report that:

[T]he Hospital has interests and responsibilities in relation to clinical trials being conducted in the Hospital, even though it is neither a sponsor of the trials nor party to contracts between external sponsors and investigators. The interest of the Hospital is both general and particular.¹⁰⁹

A finding in the Report is that the Hospital for Sick Children had opportunities to fulfil its responsibilities and defend its interests, and that there were significant instances in which the Hospital did not act.¹¹⁰

Academic freedom and support for investigator independence. The Report makes only passing reference to these important topics:

By virtue of being an academic health sciences centre, the Hospital has a general interest in promoting academic freedom and free communication. There may be differing views about whether or not the Apotex-Olivieri case was the occasion upon which to publicly “take on Apotex” on the issue of free communication. Certainly many scientists wish that had been done, not only for the sake of Dr. Olivieri, but also as a matter of principle.¹¹¹

Although it thereby acknowledged the Hospital did not effectively defend the principles of academic freedom and free communication, or Dr. Olivieri’s individual rights, the Report did not investigate and address why it did not. This is a surprising omission.

Nor did the Report investigate or address why the University of Toronto did not take effective action to defend academic freedom and investigator independence, either on behalf of Dr. Olivieri, or for the sake of the principle. It said:

For its part, the University took the view that the L1 clinical trials controversy was primarily a Hospital matter, since the University was not involved in the processes involved in the establishment, conduct or financing of the trials, and since no breach of University policy had been alleged that had not already been dealt with.¹¹²

The Review panel appears to have taken these claims by the University at face value, which is surprising in view of the documentation available to it on both the University’s involvement, and on the fact that the breaches of academic freedom by Apotex that began in 1996 had not been dealt with in an effective way. (See section 5N.)

(5) The risk of progression of liver fibrosis

The Naimark Report made an incorrect finding of fault against Dr. Olivieri—that she did not report that she judged L1 to cause “liver toxicity” to the Research Ethics Board (REB) in a timely manner.¹¹³ Although based on

erroneous information, it had significant consequences. Upon receiving the Report, the Board of Trustees passed a resolution declaring that Dr. Olivieri had “failed” in this purported reporting duty, and directed the Medical Advisory Committee to review her conduct and provide recommendations. (See sections 5P and 5Q.)

In the following, we discuss the allegations against Dr. Olivieri, and factors which led to the Review’s incorrect conclusions.

Alleged obligation to report to the REB. The fundamental premise underlying the conclusion that Dr. Olivieri had failed in a reporting obligation was incorrect. The research trials had been terminated and some patients continued on L1 under the Emergency Drug Release (EDR) program of the Health Protection Branch (HPB) of Health Canada. This arrangement did not require approval by the HSC REB. Once there was no longer a trial in place, there was no requirement to report to the REB (other than to report that trials had been terminated, which Dr. Olivieri and her clinical supervisor, Dr. Freedman did, in July 1996). Although it had documentary information that both trials had been terminated, the Naimark Review apparently relied on the incorrect information of Dr. Moore and Dr. O’Brodivich on this key point.¹¹⁴ (See subsection 5.O.2(3)). After the termination of the trials by Apotex, Dr. Olivieri had only three obligations: an ethical requirement to inform patients; a statutory requirement to inform the manufacturer of the drug; and a statutory requirement to inform the HPB. She complied with all three in a timely manner.

Alleged untimely delay in reporting. Drs. Koren and O’Brodivich alleged that Dr. Olivieri failed to report the risk of progression of liver fibrosis in a timely fashion, and based their allegations on inaccurate and circumstantial information. Dr. Koren alleged that Dr. Olivieri had presented information “related to L1 toxicity” in her talk at the meeting of the American Society of Hematology (ASH) in early December 1996, based on an inaccurate verbal account by his friend Dr. Michael Lishner.¹¹⁵ Dr. O’Brodivich cited the fact that Dr. Olivieri had submitted an abstract on the risk to a conference, and that the deadline for submission was January 10, 1997.¹¹⁶ (It is documented that the abstract was submitted past the deadline and still accepted; also, it was submitted on the basis that if the liver pathologist, Dr. Cameron was unable to confirm his tentative analysis, it would be withdrawn—see section 5K.)

Apparently reasoning from the combined information from Drs. Koren and O’Brodivich, the Naimark Report said that, “By the end of 1996, Dr. Olivieri concluded that L1 caused liver fibrosis in some patients with thalas-

semia,”¹¹⁷ and on a later page of the Report the finding of this risk was dated as having been made “in late 1996.”¹¹⁸ This was incorrect. Although some of the relevant documentation was not available to the Review, it did have some documentation that would have cast doubt on this conclusion. However, it did not refer to this documentation in its Report. The Review had the letter by Dr. Olivieri’s counsel to Apotex’s counsel dated January 14, 1997 where it was stated that no causality between L1 and progression of liver fibrosis had been identified by that date.* Although the Review did not have the benefit of the statement by the liver pathologist, Dr. Cameron, that he had not confirmed the risk until early February 1997, it had the letter by Drs. Olivieri, Cameron and Brittenham to the regulatory agencies on the risk. This letter was drafted and dated “January 22,” but Dr. Cameron refused to endorse the letter until he re-checked his analysis. He then co-signed it in early February. Unfortunately, the date of the original draft, “January 22,” was not corrected in the final letter that was sent out. Nevertheless, this was still past “late 1996.”

The Review also had Dr. Olivieri’s memo to Drs. O’Brodivich and Freedman dated March 6, 1997 in which she stated that she had informed patients of the risk on February 4. In summary, the Review did have evidence that suggested that the risk was identified in late January or early February, instead of “late 1996.” Pursuit of the discrepancy between this evidence and the allegations by Dr. Koren and Dr. O’Brodivich as to when Dr. Olivieri actually identified the risk would have revealed the truth of the matter.

The hypothesis framed by Dr. Naimark. In a November 1998 telephone conference call involving the three members of the Review panel and HSC Executive members Drs. Buchwald, Goldbloom, and O’Brodivich, Dr. Naimark “put forward a hypothesis that Dr. Olivieri may not have wished to notify the HSC’s REB in late 1996 or early 1997 because of the legal threat made by Apotex in May 1996.”¹¹⁹ Shortly thereafter, Drs. Spino and O’Brodivich wrote to him to refute this hypothesis. On November 24, 1998 Dr. Spino wrote a long letter to Dr. Naimark, alleging that Apotex had not attempted to prevent Dr. Olivieri from communicating her findings of risks. He also misrepresented Apotex’s position on Dr. Olivieri’s intention to inform the REB of the first unexpected risk of L1 (loss of sustained efficacy) in 1996.¹²⁰ (See section 5.O.2(7).) The next

*This is a letter from CMPA counsel Mr. Mason to Apotex counsel Ms. Kay, dated January 14, 1997. It was not mentioned in the Naimark Report and it was not deposited in HSC archives, but it was listed in the complete index of the Naimark Report as item #184.

day, November 25, Dr. O’Brodivich wrote a letter to Dr. Naimark in which he, too, endeavoured to refute the hypothesis.¹²¹

Dr. Olivieri promptly informed patients. The Naimark Report can be read as inferring that Dr. Olivieri had failed to inform patients promptly of the risk of progression of liver fibrosis, and that this was an issue of patient safety (see section 5P).¹²² Although it was known to several participants in the Review (including Dr. O’Brodivich) that Dr. Olivieri informed her patients in a group meeting on February 4, 1997, and there was a memo from Dr. Olivieri to Dr. O’Brodivich on this topic in the Review’s documentary base,¹²³ the Review panel did not seem to be aware of this. The group meeting was followed by individual meetings with all patients over the next couple of weeks. (See section 5K for details and citations.)

Chronic, not acute, toxicity. Drs. O’Brodivich and Koren used words and phrases in their testimony to the Naimark Review that suggested the risk of progression of liver fibrosis was one of acute toxicity. In his memo to Dr. Naimark of September 24, 1998, Dr. O’Brodivich described the situation as requiring:

An Emergency meeting (Re: patient safety related to continued use of L1 at Hospital for Sick Children)¹²⁴

and the Report said he had been “alarmed.”¹²⁵ Dr. Koren referred to “life threatening toxicity,” in a “letter” he put forward to the Review.¹²⁶ In fact, the progression of liver fibrosis observed in data of some patients did *not* arise acutely (see section 5K). Neither Dr. Koren nor Dr. O’Brodivich had expertise in the relevant fields of medicine, yet the Naimark Report appears to have accepted their incorrect characterizations of this risk.

(6) Contradictory testimony by Drs. Koren, O’Brodivich & Spino

I. A FUNDAMENTAL CONTRADICTION

Drs. Spino and O’Brodivich each gave to the Naimark Review accounts of the conduct of Dr. Olivieri in late 1996 and early 1997 that were incorrect.¹²⁷ Despite contradictory starting points, these had the joint effect of discrediting Dr. Olivieri in the eyes of the Review panel. On the one hand, Dr. Spino held (correctly) that *both* trials (LA-01 and LA-03) had been terminated, and from this he inferred that since Dr. Olivieri published data points obtained subsequent to termination, then either she had submitted a new protocol to the REB which approved it, or she was conducting unauthorized research.¹²⁸ He inferred that, if no new protocol had been

approved (which was the case), then she was doing unauthorized research. The fatal flaw in this argument was that the data points at issue came from chart review, which did *not* require REB approval, a fact published by Dr. Koren in his 1993 textbook and confirmed by the REB in April 1998.¹²⁹

On the other hand, Dr. O’Brodivich held (incorrectly) that the LA-03 trial (or perhaps both trials) had “continued” under REB jurisdiction after Apotex terminated them, citing Dr. Moore as his authority.¹³⁰ It appears that from this premise the Naimark Review deduced that Dr. Olivieri should have informed the REB of her finding that there was a risk of progression of liver fibrosis. Since she had not informed the REB, the Review concluded she had “failed” in a reporting obligation. However, the premise was simply wrong: the trials had been terminated by Apotex, which refused to reinstate the trials, as Dr. Spino understood and wrote in documents available to the Naimark Review.¹³¹ The patients who continued on its drug L1 did so under a new EDR arrangement that did not have and did not require REB approval. Therefore, Dr. Olivieri had no obligation to report to the REB.

Unfortunately, despite the contradiction between these two positions, the Naimark Review reported both (correctly) that the trials had been terminated, *and* (incorrectly) that patients remained in a continued trial and under REB jurisdiction. This contradiction is, in places, obscured by the prominence given to the inaccurate phrase, “non-renewal of Apotex sponsorship,” instead of the accurate phrase, “termination by Apotex of the trials,” which included termination of sponsorship (see subsection 5.O.2(3)).

II. DR. SPINO AND THE RISK OF PROGRESSION OF LIVER FIBROSIS

Dr. Spino attended Dr. Olivieri’s talk at the December 1996 ASH meeting. Apotex’s legal counsel then wrote to Dr. Olivieri’s counsel on December 18 asking for data that might relate L1 to liver toxicity in view of the question raised by Dr. Olivieri at the ASH meeting.¹³² Dr. Olivieri’s counsel replied in January, noting that at the ASH meeting she had not stated that L1 caused progression of fibrosis, but that if any safety concerns *were* established, she would report them to the regulators and provide Apotex with a copy of the report.¹³³ As discussed in section 5K, the new risk was not established until early February 1997 and Apotex was informed on February 4.

Thus, Apotex knew in early December that there was a question of chronic liver toxicity that would be investigated, and in early February, when the investigation was completed, it was provided with full details of the identification of the risk that L1 could cause this problem. Apotex responded to the identification in several ways. First, on February 7, through legal

counsel, it sought to confirm that Dr. Olivieri would delay reporting the new risk to regulatory agencies for a further week.¹³⁴ Second, on February 11, also through counsel, it issued a legal warning disputing that L1 posed any such risk, and saying that communication of Dr. Olivieri’s “misinformation” would “have serious and irreparable repercussions both in terms of health care and business.”¹³⁵ Third, as stated in an uncontroversial finding of the Naimark Report:

In the evening of February 18, 1997, Dr. Spino contacted Dr. O’Brodo vich to ask if he was aware of Dr. Olivieri’s opinion that she had observed “a severe adverse reaction” to the use of L1.¹³⁶

Dr. O’Brodo vich decided this required “emergency” action and intervened aggressively (see section 5K). The Naimark Review apparently did not ask why Dr. Spino waited two weeks (from February 4 to February 18) to contact Dr. O’Brodo vich, if his purpose was to alert the Pediatrician-in-Chief to a medical matter that required his attention.

On March 6 Dr. Spino wrote a letter to the senior hematologists in HSC and The Toronto Hospital (with a copy to Dr. O’Brodo vich) to advise that, “Apotex Inc. has decided to expand its compassionate use program for the drug deferiprone (L1).”¹³⁷ This letter to the hospital administrators also said, “we believe it is in the best interest of patients in Toronto to have access to the drug,” and he proposed that the administrators “designate” physicians in their thalassemia clinics willing to prescribe L1 and to sign “a confidentiality agreement with Apotex.” The letter said a treatment program had “already been successfully implemented in Italy.” However, the reference to “Italy” was to the short-term acute-toxicity trial (LA-02) whose “primary objective” was *not* to assess the long-term efficacy or safety of the drug, but rather to assess acute toxicity.¹³⁸ * The Naimark Review did not comment on why Dr. Spino informed Dr. O’Brodo vich on February 18 of Dr. Olivieri’s report of “a severe adverse reaction” to the drug, yet on March 6 he was advocating the drug be used in both HSC and TTH under an arrangement that did not specify serial liver histology assessments for all patients—the only means whereby this particular adverse reaction could be identified.¹³⁹

III. DR. KOREN’S PURPORTED “LETTERS”

The Naimark Report relied on two letters Dr. Koren submitted and reproduced them in full on page 41. They were addressed to Dr. Olivieri, signed by Dr. Koren and bore the purported dates of “December 18, 1996” and “February 8, 1997.”¹⁴⁰ In them, Dr. Koren alleged that Dr. Olivieri

*The LA-02 protocol did not specify liver histology for all participants, so was unlikely to have led to identification of progression of liver fibrosis, even if its planned one-year duration was extended. (See sections 5B and 5U.)

presented information “related to L1 toxicity” at the ASH meeting in early December 1996. From the context, the only reasonable interpretation of this allegation is that by “L1 toxicity” he meant the risk that L1 could cause the chronic-toxicity effect of progression of liver fibrosis, and that Dr. Olivieri had identified this risk by the time of her presentation at the ASH meeting. He also alleged that she had failed in an (alleged) obligation to report the finding to him, and failed to include him in the analysis of the data that led to the finding. It is open to question whether these letters were actually written and sent as Dr. Koren says. Dr. Olivieri says that she never received these letters, and it is now known that Dr. Koren acted dishonestly in regard to attempts to discredit her. Dr. Olivieri says she learned of the letters only when the Naimark Report was published, nearly two years after Dr. Koren says they were written.¹⁴¹ She alleges that they were fraudulently composed to be given to the Naimark Review in order to discredit her.¹⁴²

There is information supporting Dr. Olivieri’s claim about the two letters (see section 5R). Aside from the issue of the purported dates of Dr. Koren’s two signed “letters,” they contain incorrect and misleading information. At the time, the Naimark Review had no *a priori* reason to doubt the word of a senior scientist and administrator, and it believed the “letters.” The fact that they were quoted in their entirety in the Naimark Report shows that weight was attached to them in coming to adverse conclusions on Dr. Olivieri’s conduct.

In the second “letter” submitted to the Review, Dr. Koren said, “You have done this without me despite me [sic] being the toxicologist on the team.... I will not continue my collaborative work or data interpretation with you.” By “this” he meant the analysis of serial biopsy slides which led to the finding of the risk that L1 caused progression of liver fibrosis. The claim that at the purported time of these letters he was “the toxicologist on the team” was incorrect since there was no “team” after Apotex terminated the trials in May 1996, as Dr. Koren himself had written in other letters. For instance, a letter Dr. Koren wrote to Dr. O’Brodivich in November 1997 regarding LA-01 data said, “At that time [after May 1996] I was not any more a co-P.I. [principal investigator] with Dr. Olivieri.”¹⁴³ Earlier in 1997 he had written to Dr. Olivieri, “Because this [LA-01] study was discontinued 16 months ago May 1996]..., I... was not part of the continuing collection, analysis, or interpretation of the data.”¹⁴⁴ In May 1998, Dr. Koren wrote to Dr. Buchwald regarding data from the LA-03 patient cohort and in this memo he said that this trial had been “discontinued” in May 1996, and that he was not even “aware” that Dr. Olivieri “continued to monitor” patients who remained on L1 under EDR.¹⁴⁵ Therefore, it is quite clear from the record that Dr. Koren “no longer continue[d]” collaborative work after May 1996. Yet

he said he was a member of “the team” in February 1997, when he claimed to have written the second “letter.”

The identification that L1 caused progression of liver fibrosis in some patients required expert histological analysis and this is why a liver pathologist, Dr. Cameron, was asked to perform it. The determination of the implications for patient care required expertise in hematology, internal medicine and iron metabolism which Drs. Olivieri and Brittenham have. Dr. Koren is not an expert in any of these disciplines.¹⁴⁶

In the first of the two “letters,” Dr. Koren claimed that, “I must report on any ADR (adverse drug reaction),” implying that under the Health Canada EDR arrangement mediated by Dean Aberman, he was “the practitioner” for the EDR arrangement, in the sense of the *Food and Drugs Act and Regulations*, and thus it was he who had to report the ADR to Health Canada.* However, Dr. Koren, was not the practitioner, Dr. Olivieri was. No one could reasonably have supposed otherwise: he did not have the expertise required of a physician treating patients with thalassemia. It is evident from correspondence listed in the Naimark report’s index that both Apotex and Health Canada understood that Dr. Olivieri was the practitioner. Indeed, as Dr. Koren himself acknowledged in other correspondence,¹⁴⁷ and the Naimark Review confirmed, he was only an “intermediary in the supply chain,” or “conduit” between Apotex and Dr. Olivieri.¹⁴⁸

In the first purportedly sent “letter,” Dr. Koren wrote that, “My Israeli friend Michael Lishner attended ASH and heard your presentation... related to L1 liver toxicity.” In support of this, he provided Dr. Naimark with a letter dated December 14, 1998 from Dr. Lishner. This letter was added to the Review archives after the report was published. In it, Dr. Lishner wrote:

[At ASH] Dr. Nancy Olivieri presented her data showing that deferiprone exhibits loss of efficacy in some patients. She then went on to describe liver fibrosis associated with deferiprone therapy. I interpreted her presentation to suggest, for the first time, that L1 may cause liver fibrosis.¹⁴⁹

However, in reality, a finding that a similar chelator caused fibrosis in iron-loaded animals, and an observation that several L1-treated patients showed progression of fibrosis, suggest a question to be investigated, not a conclusion or definitive cause.

In the second purportedly sent “letter,” Dr. Koren referred to “the life threatening toxicity of the drug!” This was his interpretation, and it was *his* position that he was the person responsible for reporting “any ADR.” This raises the question: Why did he not report this “life-threatening toxicity” to

*Dr. Koren made the allegation that he was the practitioner under EDR again, and more explicitly, in the letter he wrote to the Medical Advisory Committee on December 18, 1998 (see section 5P.)

the regulators, the REB and others? By his own account, he could have done so on December 18, 1996 when he claimed to have learned of “L1 toxicity” from Dr. Lishner, or, on or about February 5, when he received Dr. Olivieri’s report on the actual identification of risk. Instead, he said nothing to anyone in authority, until he was asked about the matter on February 19 by Dr. O’Brodivich. That Dr. Koren did not report this “ADR” to anyone was confirmed by Dr. O’Brodivich in a letter to Dr. Olivieri’s CMPA counsel, Mr. Colangelo, on March 3, 1997.¹⁵⁰ The Naimark Report did not find Dr. Koren negligent in a duty to report to the REB, but found Dr. Olivieri so. It did not explain this difference.

IV. DR. O’BRODOVICH AND THE RISK OF PROGRESSION OF LIVER FIBROSIS

Dr. O’Brodivich alleged that Dr. Olivieri had failed to fulfil a purported reporting obligation. In this, he relied on incorrect information from Dr. Moore, cooperated with Dr. Koren in putting forward incorrect information, and made related allegations similar to some made earlier by Dr. Spino.¹⁵¹ His lengthy memo to Dr. Naimark of September 24, 1998 not only contained incorrect and misleading information, but omitted information in Dr. Olivieri’s favour of which he was aware. We discuss his actions during the period in question (early 1997) in sections 5K, 5P and 5Q; here we summarize matters that raise serious questions about his testimony to the Naimark Review.

After Dr. Spino contacted him on February 18, 1997, Dr. O’Brodivich became sufficiently exercised that he met with HSC legal counsel Mr. Carter to discuss whether he had a basis for disciplinary action against Dr. Olivieri. However, following meetings and correspondence during late February and early March, Mr. Carter advised that no such action was indicated “at this time.”¹⁵² One of the documents available to Dr. O’Brodivich and Mr. Carter was Dr. Olivieri’s memo of March 5, 1997 in which she invited Dr. O’Brodivich to consult independent experts in the treatment of thalassemia and iron-loading, if he had any remaining questions about her management of patient care. We have seen no evidence he ever did so. In the extensive documentary record of the period available to us, correspondence between Dr. O’Brodivich and Dr. Olivieri on this matter appears to have ceased following Mr. Carter’s advice given on March 11, 1997. Later that year Dr. O’Brodivich told Dr. Olivieri: “I consider you to be a highly successful clinician-scientist, recognized worldwide for your contributions in the area of haemoglobinopathies,”¹⁵³ and seemed to have come to the view that, instead of a risk to patients of progression of liver fibrosis, there was a scientific disagreement. In November 1997 he wrote to Dr. Spino:

Although I am not an expert in this area, I am aware that significant scientific controversy exists in regard to deferiprone’s safety and efficacy. I am confident that... the controversy will be resolved within the scientific community.¹⁵⁴

When the Board of Trustees decided to establish the Naimark Review, Dr. O’Brodivich’s view of Dr. Olivieri and the issues apparently returned to what it had been when he had been considering disciplinary action against her in February 1997. There was no new factual evidence: the case was made against Dr. Olivieri by compiling incorrect and misleading information, and by omitting pertinent correct information.

VI. DR. O’BRODOVICH’S “CHRONOLOGY” MEMO

A centre-piece of the compilation of information against Dr. Olivieri is Dr. O’Brodivich’s memo to Dr. Naimark of September 24, 1998 that was “in all likelihood” prepared with input from Dr. Koren.¹⁵⁵ The memo gives the appearance of a meticulously detailed chronology, but on close examination it is flawed. As noted earlier, it relies on incorrect information from Dr. Moore as the basis for its claim that Dr. Olivieri failed in a reporting obligation. It contains other incorrect information—for instance, that Dr. Olivieri did not inform “the thalassemia clinic’s medical staff of her concerns of hepatic fibrosis.” As we discuss in section 5P, this allegation is contradicted by documentary records.

The “chronology” has significant omissions, of which the following are examples. First, it has no entry for February 4, 1997. Dr. Olivieri held the first of her group meetings with patients that day, a fact Dr. O’Brodivich had been advised of in writing.¹⁵⁶ Second, the entry for March 6, 1997 mentions neither Dr. Olivieri’s second group meeting with patients advising that L1 should no longer be used,¹⁵⁷ nor the letter from Dr. Spino to the two hospitals promoting use of L1.¹⁵⁸ The sole entry for March 6 says that on that date Dr. Olivieri provided Dr. O’Brodivich with “guidelines for care of patients and informing parents” he had “requested on February 19.” In fact, she had provided him with the information in a letter to him on February 20;¹⁵⁹ her March 6 memo to him simply updated that information.

Third, in his “chronology” memo, Dr. O’Brodivich cited Dr. Moore’s letter to him of June 3, 1998 (he incorrectly dated the cited letter as June 3, 1997) and, although it contained fundamental errors, relied on it as evidence that a trial of L1 had continued after May 1996 so that the REB had jurisdiction.¹⁶⁰ However, he did not cite Dr. Olivieri’s subsequent letter to him (dated June 8, 1998) in which she noted that both Toronto trials had in fact been “terminated” on “May 24, 1996.”¹⁶¹ Dr. O’Brodivich also did not cite his own June 10, 1998 letter to Dr. Spino in which he referred to

communications he had just received from Dr. Olivieri, and in which he himself referred to “Apotex’s cancellation of the clinical trials in May 1996.”¹⁶² In other words, he did not cite two letters by Dr. Olivieri and himself that directly contradicted the central point in the letter by Dr. Moore—two letters written shortly after Dr. Moore’s letter.

In this memo Dr. O’Brodivich also summarized findings in the report of Apotex’s paid consultant, Dr. Francesco Callea who disputed Dr. Olivieri’s finding that L1 posed a risk of liver fibrosis: “Callea... concluded that there was a decline in the hepatic fibrosis,” in the LA-03 patients in whose data she had identified the risk.*

Dr. O’Brodivich cooperated with Dr. Koren in putting other information forward to the Review, for instance, letters written in the fall of 1998 by Ms. Naomi Klein. In these letters she made incorrect statements as to when the L1 trials ended and how long HSC patients were given L1 that were contradicted by HSC records.¹⁶³ (See section 5P(10)).

VI. THE PROPOSED STUDY OF L1 IN TREATMENT OF SICKLE CELL DISEASE (SCD)

In 1996 Dr. Olivieri had put forward for ethics review a proposal to study L1 in SCD patients. This was to be a multi-centre trial, with sites in Toronto and the United States, to study whether L1 could be helpful in removing excess iron from red cell membranes in patients with SCD (the standard iron chelator, deferoxamine, is not effective for this purpose). This proposal was still undergoing review by the REB in February 1997 and had not yet been approved. There was no plan to enrol any patients for many months and hence no issue of patient safety. The Naimark Report commented briefly on this proposed study, mainly quoting from correspondence. This matter was given greater prominence in the MAC inquiry that followed the Naimark Review (see section 5P(10) for discussion and citations).

VII. THE PERSPECTIVE OF DR. BAKER

The Toronto Hospital (TTH) evinced no concern about how Dr. Olivieri was treating patients, despite Dr. O’Brodivich’s letter of February 20, 1997 to TTH Physician-in-Chief Dr. Michael Baker expressing great concern.¹⁶⁴ Dr. Baker, who is a specialist in hematology, told us he has always had confidence in Dr. Olivieri’s management of patient care.¹⁶⁵ Dr. Baker informed Dr. Spino of this

*Dr. O’Brodivich omitted mention of the fact that Dr. Callea’s report had not been subject to peer review, unlike Dr. Olivieri’s article published in the August 13, 1998 issue of the *New England Journal of Medicine*.

confidence on April 17, 1997, in reply to Dr. Spino’s letter of March 6 promoting use of L1. The Naimark Report cited Dr. Baker’s letter, but only the paragraph in which he said none of his medical staff were willing to administer L1 in future because its safety was now in doubt, or to sign the confidentiality agreement Apotex required. In the preceding paragraph of his letter, Dr. Baker wrote:

In my view, the clinical management of patients is a matter between the attending physician and the patient... the plan of treatment proposed for patients at The Toronto Hospital who had been receiving deferiprone is being properly managed from a clinical point of view. In other words, I have no reason to question the appropriateness of the care these patients are receiving from their physicians, which as you know, does not include the administration of deferiprone.¹⁶⁶

It would have been useful for the Naimark Report to have noted the contrast between the views of Dr. Baker and Dr. O’Brodivich, and to have considered and addressed why they differed.

(7) Dr. Spino and the REB

In his November conference call with Dr. O’Brodivich and other HSC administrators, Dr. Naimark framed the hypothesis that the Apotex legal warnings might constitute a mitigating factor in Dr. Olivieri’s alleged failure to report to the REB in a timely manner.¹⁶⁷ Dr. Spino wrote a long letter to him on November 24, 1998 to refute this hypothesis. The Naimark Report accepted Dr. Spino’s argument and summarized it as follows:

Apotex did not prevent Dr. Olivieri from communicating her conclusion that there was “loss of efficacy” or “variability of response” with L1 to the REB [in the spring of 1996]. As noted earlier, Apotex “urged” her to do so (albeit after considerable debate about the interpretation of data). With respect to Dr. Olivieri’s findings of liver toxicity in late 1996, we do not know if Apotex would have attempted to prevent Dr. Olivieri from immediately reporting this serious adverse reaction to the REB. findings [sic]. Apotex has indicated the subject was not broached with them by Dr. Olivieri or her legal counsel.¹⁶⁸

Two presumptions in this quotation are incorrect: first, that there was a requirement for Dr. Olivieri to report to the REB—there was no such requirement since the trials were terminated; second, that she had made findings of liver toxicity in late 1996—such findings were not made until early February 1997.

The statements that Apotex “did not prevent” Dr. Olivieri from communicating her conclusion on the first unexpected risk to the REB in 1996, and even “urged” her to do so, need examination. It is instructive to compare Dr. Spino’s statements to Dr. Naimark in 1998 to earlier (1996 and 1997)

statements he and Apotex legal counsel made to Dr. Olivieri and others. To Dr. Naimark he wrote:

The contract does not interfere with the normal process of informing patients, investigators, REB, or regulatory agencies of *factual* concerns. ... Apotex never intended to prevent dissemination of *factual* information to the patients or the REB.¹⁶⁹ (emphasis added)

To Dr. Olivieri on May 24, 1996, he wrote:

all information whether written or not, obtained or generated by the Investigators during the term of the LA-01 Agreement and for a period of one year thereafter, shall be and remain secret and confidential and shall not be disclosed in any manner to any third party except with the prior written consent of Apotex. Please be aware that Apotex will take all possible steps to ensure that these obligations of confidentiality are met and will vigorously pursue all legal remedies in the event that there is any breach of these obligations.¹⁷⁰

In his recorded telephone message to her the same day, he said:

Nancy, I want to remind you of your confidentiality requirements under the [LA-01] contract. You must not publish or divulge information to others about the work you have done with Apotex including any data you may have gathered since April, 1993 pertaining to the use of Apotex L1 product without the written consent of Apotex. Now, should you choose to violate this agreement you *will* be subject to legal action.... we have every intention of bringing it (L1) to market as soon as possible.... The thalassemic community (the patients and their families) will be informed. We will do that but you are not to communicate your misinterpretations ...¹⁷¹ (emphasis added)

Dr. Spino himself underlined “all” in his May 24, 1996 letter and while this statement was issued in the context of the findings of loss of sustained efficacy, “all” means all. A few weeks later he confirmed Apotex’s position in writing, “...we could not allow such information to be transmitted to patients...,”¹⁷² and he made a similar statement in a letter to the editor of *The Medical Post* published on February 18, 1997 (see section 5F).

As for Dr. Spino’s “urging” of Dr. Olivieri to communicate her findings to the REB, a review of his 1996 correspondence with Dr. Olivieri, Dr. Koren, Dr. Zlotkin and others was provided in section 5E, but for convenience we summarize it here. In early February 1996, Dr. Olivieri insisted that the REB must be informed of a new risk (loss of efficacy). Dr. Spino responded by proposing that raw data be reported to the REB, without Dr. Olivieri’s analysis and conclusions, but with Apotex’s view of the data instead.*¹⁷³ This would have been an empty gesture, because no member of

*Dr. Spino wrote to Dr. Olivieri, “We believe it is premature to conclude there is a change in efficacy or to imply such to the Human Subjects Review Committee [REB].” (February 14, 1996)

the REB had the expertise to interpret the data. It would have been a failure on her part to fulfil her ethical obligations in a clinical research trial: she would have failed to communicate that she had identified a risk. Dr. Olivieri then made it quite clear that she would provide the REB with her analysis of the data and her conclusions, regardless of whether Apotex agreed with her action. In reply, Dr. Spino wrote, “the decision to present the information to the Ethics Committee [REB] is yours and we urge you to do so, if you feel it is warranted.”¹⁷⁴ However, it is clear from subsequent correspondence that, while on the surface accepting Dr. Olivieri’s decision to advise the REB, Dr. Spino in fact then proceeded to make an end run to influence the REB not to accept her advice that patients should be informed of a risk.

After Dr. Olivieri sent the REB a formal report on her findings of loss of efficacy, Dr. Spino wrote to the REB presenting the Apotex view and offering to meet with the REB. When this overture was rebuffed by Dr. Zlotkin, the REB Chair, Dr. Spino wrote to Dr. Koren (who had been succeeded as REB Chair by Dr. Zlotkin) suggesting that he might wish to intervene with the REB.¹⁷⁵ A few weeks later, Dr. Spino wrote another letter to the REB, to the effect that Apotex had matters in hand “and no further action by Dr. Olivieri at this time is warranted.”¹⁷⁶

Thus, while in February 1996 Apotex “urged” Dr. Olivieri to report to the REB, it also asked her to report the data without her medical interpretation that there was a risk, and later it urged the REB not to act on her information. By early May Apotex was, in effect, suggesting to the REB that Dr. Olivieri did not need to inform patients, by asserting that “no further action... is warranted.” On May 10, 1996 Dr. Zlotkin again rebuffed Dr. Spino, advising that, “My mandate is to protect study subjects and patients and to that end must ensure full disclosure when unexpected study findings are identified,” that it was not his role “to act as intermediary between the investigator and sponsoring company on issues pertaining to science,” and that “I... have reminded the principal investigator [Dr. Olivieri] to revise the clinical information and consent forms appropriately....”¹⁷⁷ When Dr. Olivieri submitted the new forms on May 20, Apotex revealed its real intent, to prevent patients from being informed. It immediately terminated the trials and issued the warnings to Dr. Olivieri not to disclose “any information in any manner to any third party,” including patients, or she would be subject to legal action.¹⁷⁸

On the issue of whether Apotex attempted to deter Dr. Olivieri from informing the REB of the second risk in February 1997, the Naimark Report, apparently relying on Dr. Spino’s letter to Dr. Naimark of November 24, 1998, said:

the subject was not broached with them [Apotex] by Dr. Olivieri or her legal counsel.¹⁷⁹

However, the documentary evidence is clear that when this second risk was identified, counsel for Dr. Olivieri forwarded her report to counsel for Apotex with a covering letter saying:

Dr. Olivieri intends to report safety concerns to the *relevant authorities* directly and thus she is giving advance notice of her intention to do so to Apotex by this letter.¹⁸⁰ (emphasis added)

As noted earlier, it was the position of Dr. Spino that Dr. Olivieri conducted research on the patients after Apotex terminated the trials, so that on this premise the “relevant authorities” would have included the REB. Therefore, although he was incorrect (she was not conducting research on the patients and there was no obligation to inform the REB), by his own logic, the subject had indeed been “broached with” Apotex. Dr. Spino concluded his letter to Dr. Naimark with the statement:

Apotex did not threaten Dr. Olivieri, and did not advise her not to tell her patients or the REB about her alleged findings on deferiprone-exacerbated hepatic fibrosis.¹⁸¹

This was untrue. Apotex’s response to Dr. Olivieri’s report on the risk of progression of liver fibrosis was to issue a legal warning. This letter, dated February 11, 1997, warned her not to communicate this finding and included such phrases as: “it would be a travesty to frighten patients and their doctors with such mis-information,” and “Apotex will contest the right of your client to publish the information in light of her obligations to confidentiality under various contracts.”¹⁸² It is relevant to note that the original written warning from Apotex (dated May 24, 1996) has never been rescinded, and that letter warned Dr. Olivieri she was not to disclose *any* information about L1 to anyone, except with Apotex’s prior written consent.¹⁸³

In summary, Apotex’s position was that no one, whether patients, the regulators, other physicians treating thalassemia patients with L1, the REB, or medical administrators should be informed of this risk, except with its prior written permission—permission that has never yet been given. Further, should Dr. Olivieri do so, she would be subject to legal action by Apotex. Therefore, it is hard to understand why the Naimark Review believed Dr. Spino’s letter of November 24, 1998 saying the company had not attempted to impede Dr. Olivieri from communicating her findings of the two unexpected risks of L1.

(8) Dr. Olivieri’s response to the Report

On December 9, 1998 the Hospital released the Naimark Report and announced that the Board of Trustees had referred the Report’s adverse finding against Dr. Olivieri to the Medical Advisory Committee, which advises the Board on staff disciplinary matters (see section 5P). On the following day, Dr. Olivieri issued a statement that the finding that she had “failed to report [her] concerns about liver toxicity to the Research Ethics Board in a timely fashion” was “at odds” with the facts.¹⁸⁴ She noted that those patients who had continued on L1 after Apotex terminated the two trials in May 1996, “were then no longer treated in the setting of a ‘clinical trial,’” and instead were treated under Health Canada’s Emergency Drug Release Program(EDR).¹⁸⁵ Thus she had no obligation to report to the REB. She explained that under EDR her obligations were to inform patients, Apotex and Health Canada, and that she fulfilled these in a timely fashion.

Dr. Olivieri alleged:

the Hospital has determined that, rather than looking in the mirror, they would close ranks and lay blame on my shoulders for a number of issues.¹⁸⁶

She said that the “bias” of the Naimark Review could be seen in its Report, and that a review of all of the relevant information and documentation would have to wait for “a truly independent inquiry.”¹⁸⁷

(9) Conclusions

1 | The Report made a number of significant policy recommendations and these led to subsequent policy reviews by the Hospital and the University. An important matter discussed in the Report but not yet addressed is provision of a grievance and arbitration procedure for HSC medical and scientific staff in regard to their HSC employment.

2 | The Report’s account of events and circumstances of the L1 controversy is incorrect in fundamental respects. In particular, the Report erroneously supposed that a research trial of L1 continued after both trials had been terminated. Therefore, contrary to the Report’s conclusion, the REB had no jurisdiction over those patients who continued on L1 under EDR after the terminations of the trials, and Dr. Olivieri in fact had no obligation to report to the REB.

3 | The Review was misled through a combination of incorrect and incomplete information. Dr. Koren, Dr. O’Brodivich, Dr. Spino and Dr. Moore are principally responsible for the incorrect information. The responsibility for

the Review apparently not having been provided with a number of relevant documents rests with a larger number of persons who participated in the Review, as well as with Dr. Olivieri who did not participate.

4 | The Naimark Review panel members themselves must bear some responsibility for their incorrect conclusions, because they did not pursue and resolve some important discrepancies in the information that was provided to them. Prominent among the discrepancies was testimony by Dr. Moore and Dr. O’Brodivich that a research trial of L1 continued after May 1996, which was contradicted by documentary evidence considered by the Review from Dr. Spino of Apotex, Dean Aberman, Dr. Koren and others, as well as documentary evidence originating with Dr. Olivieri that was put forward by others. Had they pursued these discrepancies they may well have been led to quite different findings. That they did not do this may have been related to the short time frame provided by the Hospital Board for the Review.

Review panel members did not have the advantage of knowing that a major player, Dr. Koren, had been acting dishonestly in attempts to discredit Dr. Olivieri during the period of the Review (as well as later). They therefore so did not have a high index of suspicion to analyse and double check his testimony, as well as other testimony given to them by persons closely associated with him.

5 | The Report’s adverse findings in regard to Dr. Olivieri are not valid. However, they led the Board of Trustees to the incorrect belief that she had “failed” in a reporting duty. The Report and actions taken by HSC on the basis of the Report have caused serious harm to her reputation. They have necessitated her devoting much time and personal resources to defending her reputation and career. The Report’s adverse conclusions have since been invoked by Apotex to defend the reputation of its drug L1.¹⁸⁸

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5P | The Medical Advisory Committee Proceedings

(1) Overview

IN DECEMBER 1998, upon receipt of the Naimark Report, the HSC Board of Trustees initiated an inquiry by the Medical Advisory Committee (MAC) into Dr. Olivieri's conduct during late 1996 and early 1997. The MAC is the body empowered to advise the Board on disciplinary action against staff physicians and it was directed to consider the "failure" by Dr. Olivieri in two specified matters, and to provide the Board with "conclusions and/or recommendations."¹

An *ad hoc* "fact finding" subcommittee of the MAC invited Dr. Olivieri and other persons to "provide assistance in obtaining information."² Several witnesses provided written and oral testimony from December 1998 to February 1999, with Dr. Koren and Dr. O'Brodovich providing the most extensive testimony. The subcommittee then sent a list of five questions to Dr. Olivieri.³

Dr. Olivieri informed the subcommittee through legal counsel that she was "prepared to co-operate fully with the investigation," and asked to be provided with the allegations and testimony the committee received from persons appearing before it, so she might prepare her response.⁴ The subcommittee did not grant this request, but continued to require that she respond to its questions without this information.

The documentary record shows that the only relevant information available to Dr. Olivieri as to the basis of the five MAC questions were: the Board directive to the MAC; the Naimark Report and the subset of its documentary base deposited in the HSC library archive; and the five questions. She had no knowledge of certain allegations made by Drs. Koren and O'Brodovich and others to the Naimark Review, because a number of relevant documents relied on in the Review were not deposited in the HSC library archive (some but not all of these "were provided to Dr. Naimark in confidence" and not made available⁵). Nor was she informed of *new* allegations made by Drs. Koren and O'Brodovich to the MAC's subcommittee.⁶ In October 1999, Dr. Olivieri provided a detailed written response to the five questions with extensive supporting documents, but this was without the benefit of knowledge of the allegations and testimony made against her.⁷

After receiving Dr. Olivieri's response, the MAC subcommittee made an (undated) written report to the full MAC. Except for one part of one question, the subcommittee did not accept Dr. Olivieri's answers to any of its five questions. In mid-January 2000, MAC Chair Dr. Laurence Becker forwarded this report to Dr. Olivieri, with a covering letter endorsing the report on behalf of the full MAC. His letter set out the same five questions as in the

report, along with an accompanying set of “concerns,” and requested that Dr. Olivieri meet with the MAC itself to respond.⁸

The report of the subcommittee made clear that undisclosed allegations had been considered. It was also clear that the subcommittee made errors of fact and interpretation in its report. These could have been avoided had the subcommittee exercised proper diligence in reviewing Dr. Olivieri’s submission of October 1999, and disclosed to her all allegations. These errors were not corrected by the full MAC.

Dr. Olivieri requested (directly, and through counsel) disclosure of all allegations and relevant information, in letters to the MAC, to the Hospital, and to Dr. Naimark.⁹ After further legal representations, she received some documents on March 10, 2000,¹⁰ five months *after* she had submitted her response to the subcommittee and two months *after* that committee reported. Yet the allegations and related testimony had been placed before the subcommittee more than a year earlier.¹¹

Prominent among the undisclosed allegations were that liver biopsies done on some of Dr. Olivieri’s patients were not clinically indicated, but had been done simply for research purposes.¹² This was not the case: the related testimony contained serious errors, in which standard monitoring of thalassemia major patients for therapeutic purposes in managing their care was misrepresented as research. Since this had not been addressed in the Naimark Report, in the Board resolution, or any other documentation available to her, Dr. Olivieri could not have anticipated that *behind* the MAC’s questions lay a series of new allegations by Drs. Koren and O’Brodivich.

Some other allegations made both to the Naimark Review and the MAC inquiry were also incorrect—for instance, the allegation that a research trial of L1 had continued after Apotex terminated both Toronto trials.

Dr. Olivieri was denied the opportunity to be accompanied by legal counsel in an appearance before the MAC.¹³ Because the documentation that Dr. Olivieri finally received from the MAC in March 2000 was substantially incomplete, her counsel again renewed the request for full documentation so that Dr. Olivieri could have a fair basis to make her case. Her counsel suggested the unreasonableness of the MAC procedure would be clear to the courts and requested that the MAC revise its procedure so as to provide full disclosure and a fair opportunity to respond.¹⁴ The MAC did not provide the requested information and instead concluded its proceedings, recommending to the Board that its allegations (cast in the form of “concerns”) about Dr. Olivieri’s conduct be referred to the College of Physicians and Surgeons of Ontario (CPSO) and the University of Toronto. The Board approved this recommendation and in a press conference held on April 27, 2000, the MAC and the Board

publicly announced the referrals of “patient care” concerns to the CPSO and “research” concerns to the University.¹⁵

(2) The Board’s directive to the MAC

The Medical Advisory Committee (MAC) is advisory to the Board of Trustees of the Hospital and responsible to the Board for matters involving medical care and medical staff, including:

- the quality of medical and dental care provided in the Hospital;
- appointment or re-appointment to the staff and the privileges to be granted to each member of the staff;
- the dismissal, suspension or restriction of privileges of any member of the staff.

On the same day the Naimark Report was made public, December 9, 1998, the Board passed the following resolution:

The Board directs the MAC to consider the failure of Dr. Nancy Olivieri to report her concerns related to L1 toxicity to the Research Ethics Board, both in respect of the then current use of L1 under the Compassionate Release Program* and Dr. Olivieri’s then pending application to have L1 approved for the treatment of sickle cell disease and any other related matter; and, for this purpose the MAC may appoint an Ad-hoc Committee of its members pursuant to Section 23.02 of the Hospital by-laws.

The MAC is to report to the Board its conclusions and/or recommendations as soon as practicable.¹⁶

A list of members dated January 2000 included Mr. Strofolino, Drs. Goldbloom, O’Brodivich and Buchwald and nineteen other Hospital staff holding administrative positions, with Dr. Laurence Becker as Chair and Dr. Ronald Laxer as Vice-Chair. In its press conference of April 27, 2000 the Hospital stated:

[The MAC] is an impartial and fair body made up of Dr. Olivieri’s peers. This MAC report is its own—not the administration’s and not the Board’s.... To ensure that all of the proceedings and findings were unbiased, members of Sick Kids’ MAC who had significant involvement in the L1 issue including the President and CEO of the Hospital and the Chiefs of Research and Paediatrics, excluded themselves from these deliberations.¹⁷

Nevertheless, the proceedings were characterized by unfairness of the most fundamental and obvious kinds. As noted above, the case against Dr.

*This is the Emergency Drug Release (EDR) program of Health Canada. Contrary to the supposition underlying the Board resolution, the EDR arrangement for treatment of patients with L1 after the research trials were terminated in May 1996 was not under REB jurisdiction (see sections 5G(1), 5H(1), 5J and 5K(7)).

Olivieri was not disclosed to her and she was not provided with a fair opportunity to respond. Also, the language in the Board’s resolution was not neutral. Rather than asking the MAC to consider why Dr. Olivieri did not report to the REB, it stated there was a “failure” in a purported duty to report. It was not sufficient to simply rely on the Naimark Report, because Dr. Olivieri had not participated in that Review so that its Report was primarily based on information and interpretations advanced by one side. Also, the two MAC witnesses who put forward the most extensive allegations and testimony against Dr. Olivieri, and who were the most senior in rank and administrative authority, Dr. Koren and Dr. O’Brodivich (the Pediatrician-in-Chief), were biased against Dr. Olivieri, as their documented participation in the Naimark Review shows. (See sections 5O and 5R.) Other witnesses who made allegations against Dr. Olivieri to the MAC were closely associated with Dr. Koren (see below).

It is relevant that before the MAC completed its proceedings in late April 2000, Dr. Koren had been disciplined for “gross misconduct,” including “lying,” in connection with anonymous letters disparaging Dr. Olivieri that he had sent to a newspaper and various individuals. He sent these letters during the period of his participation in the Naimark Review and the MAC proceedings. We have no evidence that either the MAC or the Board investigated the validity of Dr. Koren’s allegations to the MAC, or the possible influence his allegations had on the material Dr. O’Brodivich and other witnesses put forward.

(3) The MAC subcommittee

The *ad hoc* subcommittee originally consisted of five members, reduced to four when one member was perceived to be in conflict of interest.¹⁸ The subcommittee then consisted of Chair Dr. L. Roy (Chief, Anaesthesia), Dr. G. Barker (Chief, Critical Care Medicine), Ms. A. MacIntosh-Murray (Director, Quality Management) and Dr. C. Harrison (Director, Bioethics).

The subcommittee attempted to correct the problem introduced by the Board resolution by writing to Dr. Olivieri:

The MAC is of the view that the word “alleged” should appear before the word “failure” in the first line of the resolution and the MAC interprets the resolution that way.¹⁹

Dr. Roy assured Dr. Olivieri:

At the moment, the MAC only intends to consider the specific issues set out in the resolution. During the course of its consideration, other “related matters” may arise. If those are to be considered, you will be notified.²⁰

As it happened, the subcommittee and the MAC *did* consider other matters but, contrary to Dr. Roy's written assurance, Dr. Olivieri was *not* notified. The Board resolution referred specifically to "failure... to report... L1 toxicity to the REB." One of the principal witnesses, Dr. O'Brodovich, opened his letter to the MAC with a statement that makes it clear that the *ad hoc* subcommittee both invited and accepted testimony on other related matters:

I have followed the Board's Resolution to the MAC: i.e. in my submission I not only discuss the apparent failure of Dr. Nancy Olivieri to report her concerns related to L1 toxicity to the Research Ethics Board but also to any related matter; in your letter you state that "*other 'related matters' would be matters of patient care which are linked to the specific issues referred to in the resolution.*"²¹ (emphasis in original)

(4) The five "questions"

On February 16, 2000, after interviewing several witnesses, the subcommittee forwarded a series of questions to Dr. Olivieri:

1. When did individuals receiving L1 in the LAO3 Trial cease to be "subjects of research"? When did individuals receiving L1 in the LAO1 Trial cease to be "subjects of research"?
2. When did you report your conclusions regarding the toxicity of L1:
 - a) to the Research Ethics Board;
 - b) to patients and parents using L1;
 - c) and to colleagues prescribing L1?
3. Did you continue to provide L1 to patients after you concluded that it was "toxic"? If so, why?
4. Did your application (January 1997) to the Research Ethics Board for approval of the study "to examine the effects of L1 in patients with sickle cell disease" include information about risk of hepatic damage or cirrhosis associated with the administration of L1?
5. Did you schedule liver biopsies for patients receiving L1 in February, March, and April 1997? If so, why?²²

Issues raised by these questions are discussed below and in sections 5K and 5Q. The subcommittee was satisfied with only one of Dr. Olivieri's answers (to subquestion 2 b)). The MAC itself repeated all these questions to her in January 2000, together with an accompanying set of "concerns."

(5) Dr. Olivieri's response

Dr. Olivieri received no reply to her January 1999 request²³ for access to the information considered by the subcommittee, other than a demand that she respond to the five questions as posed. Without benefit of full information on

the allegations against her, she submitted her response to the committee's questions on October 12, 1999 in the form of a lengthy brief and three volumes of supporting documents indexed to her brief.²⁴ Prepared with the assistance of legal counsel, the brief outlined the history of the L1 trials and the post-trial period in which L1 was administered under Emergency Drug Release. It endeavoured to provide answers to the five questions, in the full medical and administrative context.

Reporting to the MAC, the *ad hoc* committee characterized Dr. Olivieri's response in the following general terms:

The response (three volumes) dealt with a number of extraneous issues. Members of the committee however elected to review the material and extract from these volumes any material which pertained to the questions described above.²⁵

In our considered opinion, the response provided clear and correct answers to the stated questions. Where a short and direct answer was indicated, such an answer was in Dr. Olivieri's brief. For instance, after explaining the contractual, HSC policy, and regulatory contexts, she answered question 1, on when individuals ceased to be subjects of research, as follows:

Therefore, after May 24, 1996* these thalassemia patients at HSC ceased to be subjects of the clinical research trials LA-01 and LA-03 but instead became patients of Dr. Olivieri who was, and remains, responsible for their clinical care. Dr. Olivieri cared for and continues to care for these patients using the clinical protocols she has developed** for thalassemia and iron overload.²⁶

Where a matter was complex, Dr. Olivieri provided a detailed explanation with reference to supporting documents. For instance, her answer to question 4, on the proposed study of L1 in patients with sickle cell disease, was detailed in an effort to ensure that the members of the subcommittee (none expert in either this disease or thalassemia) understood the necessary medical and scientific background.²⁷

The brief stated that Dr. Koren had provided the Naimark Review with incorrect and misleading information against Dr. Olivieri. It also noted a series of anonymous letters disparaging her and her supporters during 1998 and 1999, and said that in May 1999 a complaint had been filed with the HSC administration against an individual on the basis of forensic evidence. This

*This was when Apotex terminated both trials and (on the next working day) withdrew all supplies of the drug L1 from the HSC pharmacy (see letter, Spino to Olivieri and Koren, dated May 24, 1996).

**Therapeutic protocols developed by Dr. Olivieri were published in review articles in leading journals: N. Olivieri and G. Brittenham, *Blood*, 89, 3 (February 1, 1997); N. Olivieri, *The New England Journal of Medicine*, 341, 2 (July 8, 1999). The more detailed review in *Blood* had been submitted to the journal in February 1996, and a copy of the published article was included in her October 12, 1999 submission to the MAC.

was Dr. Koren, who was not accused in the brief of being the author of the letters, on legal advice, since he had been denying responsibility and the investigation into the complaint had not been concluded. In December 1999, after being identified by DNA evidence, Dr. Koren admitted to authorship of the letters, thereby acknowledging he had been lying about his conduct for many months, a development that was announced in the Hospital and received extensive media coverage. (See section 5R.)

A properly conducted inquiry would regard it as highly relevant that a witness had been found to have dishonestly attempted to discredit the person whose conduct was the subject of the inquiry. This would normally raise questions about the accuracy and truth of the testimony given by that witness. It would also be a signal to be alert that other witnesses associated with him, who provided information supportive of his testimony, may have been misled by him. It is therefore surprising that, despite the fact that Dr. Koren's misconduct was widely publicized in December 1999—a month before the *ad hoc* subcommittee and the MAC issued their January 2000 reports—the MAC did not appear to heed these warning signals. We have seen no evidence that they objectively and critically evaluated the testimony of Dr. Koren and other witnesses associated with him.

(6) Limitations of the MAC review

Why did the fact-finding subcommittee and the MAC not accept Dr. Olivieri's answers to the five questions? In the following subsections we examine the available evidence as to what occurred, and on this basis conclude that it is probable that several of the following possible reasons were relevant:

- They were misled by incorrect allegations and testimony from Drs. Koren and O'Brodovich and other witnesses.
- They did not exercise proper diligence in considering the facts in Dr. Olivieri's three-volume response.
- None of the members of the subcommittee or of the full MAC was expert in the relevant field of medicine, and they did not consult any independent experts, so may not have fully understood Dr. Olivieri's answers to some questions, particularly if they did not exercise proper diligence.
- They were misled by incorrect statements by Dr. Moore on REB status.
- Since the allegations and information of witnesses were not disclosed to Dr. Olivieri, they deprived themselves of the opportunity of having

misinformation on medical procedures and other matters brought into the open and corrected.

The members of this Committee of Inquiry are not experts in the relevant fields of medicine. However, we carefully reviewed Dr. Olivieri's October 1999 brief to the MAC, which was written for non-experts, and we followed up on her references to the more than one hundred supporting documents appended to that brief. We asked Dr. Olivieri for additional references to the relevant medical literature, which she then provided. The relevant findings and recommendations in the literature are understandable by any reader who makes an effort to learn the meaning of a modest amount of specialized terminology (see, for instance, the quotation opening our section 5Q).

(7) Connections among MAC witnesses

According to the report transmitted to Dr. Olivieri on January 18, 2000, the subcommittee of the MAC interviewed five persons in early 1999: Dr. Zlotkin, Dr. Moore, Dr. O'Brodovich, Dr. Koren and Dr. Patricia Massicotte.²⁸ Dr. Olivieri subsequently learned that Dr. Gordana Atanackovic was also interviewed.²⁹

About ten days before the subcommittee's report was transmitted to Dr. Olivieri, Dr. Laxer, Vice-Chair of the MAC, received a letter from Dr. Matitiahu Berkovitch elaborating on certain allegations he had made to the Naimark Review.³⁰ After receiving this letter, Dr. Laxer responded to Dr. Berkovitch, asking if he could provide the letter to his colleagues on the Medical Advisory Committee, and adding:

The MAC has been asked to investigate for the Board whether some of Nancy's practices were 'research' as opposed to 'clinical care'.³¹

This construction of the Board's directive of December 9, 1998 had not been disclosed to Dr. Olivieri, yet the distinction made by Dr. Laxer was central: it underlay the MAC questions. Prominent among the incorrect allegations made to the MAC were those by Drs. Koren and O'Brodovich to the effect that standard clinical monitoring of patients with thalassemia major was "research," allegations that were not disclosed to Dr. Olivieri.

As part of his written testimony to the *ad hoc* committee, Dr. O'Brodovich put forward allegations against Dr. Olivieri that Dr. Atanackovic and Dr. Berkovitch had put forward in the Naimark Review, but which were not discussed in the Naimark Report.³² The letters Drs. Atanackovic and Berkovitch wrote to Dr. Naimark were not deposited in the HSC library archive of documents from his Review. In March 2000 these letters were said by HSC legal counsel to have been "provided to Dr. Naimark in confidence," when he

refused to provide copies to Dr. Olivieri.³³ Yet, a year earlier, Dr. O’Brodivich had quoted from these letters and provided copies to the MAC.³⁴

Dr. O’Brodivich also relied on letters by Ms. Naomi Klein he had put forward during the Naimark Review. In these letters, Ms. Klein stated that the trials continued until May 1997, and that L1 was administered to HSC patients until then. This information is documented to be incorrect (see section 5.O.2(6) and below).

Connections among Drs. Koren, O’Brodivich, Massicotte, Atanackovic, and Berkovitch, and Ms. Klein are relevant to our discussion.

Drs. Atanackovic and Berkovitch were research fellows in Dr. Koren’s HSC Division, Clinical Pharmacology and Toxicology, recruited by him and assigned to the L1 trials as part of their work. For that work they were supervised both by Dr. Olivieri and Dr. Koren. Dr. Berkovitch was at HSC during 1992–1994, then returned to Israel. Dr. Atanackovic commenced her fellowship during the period of the Apotex sponsorship of the trials. She came under Dr. Koren’s sole supervision after the trials had been terminated, and was still employed with him during the time of the Naimark Review and MAC proceedings. Drs. Atanackovic and Berkovitch provided incorrect information to both the Naimark Review and the MAC (discussed below).

Ms. Klein, the daughter of one of Dr. Koren’s assistants, worked as a data manager for administration of L1 during the trials and during the subsequent non-trial EDR arrangement.

Dr. Patricia Massicotte was a research student of Dr. O’Brodivich’s wife, Dr. Maureen Andrew O’Brodivich, at McMaster University. In 1996 Dr. O’Brodivich terminated the employment of Dr. Olivieri’s assistant, Dr. Eric Nisbet-Brown, and appointed Dr. Massicotte to replace him.³⁵ She subsequently worked part-time as a physician in the HSC thalassemia clinic, while continuing to assist Dr. Maureen Andrew O’Brodivich in research. During the Naimark Review, Dr. Hugh O’Brodivich attested that “the thalassemia clinic’s medical staff” were not informed by Dr. Olivieri of “her concerns of hepatic fibrosis” prior to February 19, 1997 when he himself informed them. He cited Dr. Massicotte as his source of information.³⁶ In fact, there is documentary evidence that Dr. Massicotte was informed in late January 1997 (see below). It is possible Dr. O’Brodivich may have misunderstood the situation.

The four witnesses who made allegations against Dr. Olivieri on medical matters were Drs. Koren, O’Brodivich, Atanackovic and Berkovitch. None of them is an expert in the treatment of patients with thalassemia major. The particular link among them is provided by Dr. Koren, and each of Drs.

O’Brodivich, Atanackovic and Berkovitch have been associated with Dr. Koren in actions adverse to the interests of Dr. Olivieri.

Ms. Humphrey, the Hospital’s harassment investigator, concluded that “in all likelihood” Dr. O’Brodivich’s September 24, 1998 memo to Dr. Naimark, highly critical of Dr. Olivieri, “was prepared with input from Dr. Koren.”³⁷ Purporting to provide a detailed chronology of events during 1996–1997, this memo had significant omissions and contained incorrect information against Dr. Olivieri. It is documented through correspondence that Drs. Koren and O’Brodivich cooperated in bringing forward other incorrect information to the Naimark Review, including letters they obtained from Ms. Klein and an allegation that Dr. Olivieri’s 1997 ASH abstract showed that she continued to administer L1 to HSC patients until May 1997. (See section 5.O.2. and below.) In the documentary record of the MAC inquiry, Drs. Koren and O’Brodivich referred to each other’s correspondence, and made similar allegations.³⁸

Apotex financial support for Dr. Koren’s research included salary support for Dr. Atanackovic as a research fellow under his supervision, during and after the trials. Dr. Atanackovic is a co-author with Dr. Koren of a 1999 journal article on the efficacy of L1 based on data from the LA-03 trial. The article did not disclose financial support by Apotex for the work, did not acknowledge Dr. Olivieri’s contributions to generating the reported data, and did not note previously published findings of risks of L1. (See sections 5G and 5R.)

As a research fellow in Pediatric Pharmacology from July 1992 to June 1994, Dr. Berkovitch worked on aspects of the L1 trials, and was a co-author with Dr. Olivieri on articles involving joint work.³⁹ He has continued to publish research with Dr. Koren. In 2000, Dr. Berkovitch published an article using data from the LA-01 trial for which Dr. Olivieri was principal investigator—the trial co-sponsored by Apotex and MRC.⁴⁰ The article included Dr. Olivieri’s name in the list of co-authors. In May 2000 Dr. Olivieri reported to this Committee that she had not been consulted on this publication, and that the use of trial data, as well as the listing of her name among the authors, was without her knowledge or consent.⁴¹ Thus her name was used, but she had no opportunity to comment on the analysis with which she was now associated by listing her as a co-author. The written policy of the publisher of the *Journal of Pediatric Endocrinology and Metabolism* is that all authors must sign a release of copyright. Dr. Olivieri reported to us that she did not sign such a form. Dr. Berkovitch is given as the lead author of the article, with “co-authors” Dr. Koren and Dr. Steve Milone, as well as Dr. Olivieri and others. Like Dr. Olivieri, Dr. Milone had no prior knowledge of this publication and did not consent to it.⁴² It is also of note that the article does not acknowledge

the financial support for the LA-01 trial by MRC or Apotex, contrary to widely accepted guidelines for publication in the biomedical field.⁴³ We do not know of Dr. Koren's position on the matter of this publication.

(8) Allegations by Dr. Berkovitch & Dr. Atanackovic

In the letters they each wrote to the Naimark Review in the fall of 1998, Drs. Berkovitch and Atanackovic made allegations against Dr. Olivieri's conduct during the period of the trials (before May 24, 1996).⁴⁴ The Naimark Report did not discuss their allegations, and the MAC appears ultimately not to have pursued them, possibly because they were contradicted by documentary evidence. They are of interest, however, because they were put forward by Dr. O'Brodovich in his written testimony to the MAC,⁴⁵ even though the documentary evidence establishing that they were incorrect was available to him. Thus, they are additional instances in which Dr. O'Brodovich put forward allegations against Dr. Olivieri that had also been put forward by Dr. Koren or persons associated with him, apparently without checking their validity against available documents (see sections 5P(10) and 5Q).

Dr. Atanackovic alleged to the Naimark Review that Dr. Olivieri had improperly enrolled two patients in the randomized comparison trial (LA-01), in that their hepatic iron concentrations (HIC) were too low. However, the LA-01 protocol approved by the REB set no limits on HIC at enrolment, so her allegation was incorrect.⁴⁶

Only the summary of Dr. Atanackovic's oral testimony to the MAC is available. The summary is vague and ambiguous, and it is not clear whether she made any allegations against Dr. Olivieri in her meeting with MAC members. However, the summary contains incorrect information to the effect that those patients who had been enrolled in the LA-01 and who continued on L1 under EDR after the trial terminations, were not monitored after May 1996, and that those who had been in LA-03 were monitored only for white blood cell counts and compliance with their drug administration schedule. As discussed in sections 5G, 5H, 5J, 5K, 5Q and 5R, it is documented that all patients who continued on L1 under EDR were monitored by the same tests as during the trials (for instance, determination of hepatic iron concentration) and the results recorded.⁴⁷

Dr. Berkovitch made two allegations in his letter to the Naimark Review. The first was that patients enrolled in the long-term trial (LA-03) had liver biopsies that were not specified in the protocol and were not clinically indicated, but instead were improperly done for research purposes. Dr. Berkovitch repeated this allegation to the MAC, identifying the two patients by a code used in documents available to the Naimark Review. Dr. Olivieri's report to the

regulators in early 1997 shows that this allegation was not correct (Dr. O’Brodivich, Dr. Koren and the MAC all had copies of this report—see sections 5K, 5Q and below).⁴⁸ One of these two patients had only two biopsies, separated by a year, as specified in the protocol. The other patient had experienced significant progression of liver fibrosis during a one-year interval, a serious matter providing clinical indication for a follow-up biopsy several months later. Thus, the allegation was incorrect.

Dr. Berkovitch’s other allegation to the Naimark Review was that Dr. Olivieri was personally abusive to colleagues, research fellows and support staff during the period of his research fellowship in Toronto (1992–1994):

All the staff on this project, without any exception had bad relationships with Dr. Olivieri.⁴⁹

However, three years earlier, in 1995, Dr. Berkovitch had written to Dr. Haslam, the Chair of Pediatrics, supporting Dr. Olivieri’s early promotion to the rank of professor, and stated:

During these two years of fellowship, I worked with Dr. N.F. Olivieri, and I had a great opportunity to know her. The Haemoglobinopathy programme, under the supervision of Dr. Olivieri, was a very warm, friendly, and academic place to work. The relationship between the physicians and the patients, and among the staff were very good. We had a nice and familial atmosphere in the clinic. From an academic point of view, this fellowship was the climax of my academic career. With the high motivation and great enthusiasm of Dr. Olivieri, the research programme was advanced, profound and successful. Dr. Olivieri gave me the tools and the knowledge how to conduct a study, and how to write an article. I was lucky to participate and to be part of her research group, and with her support and help I published an article in “The Lancet”... [and] ...another article, this time in “The New England Journal of Medicine.”... Thanks to these publications, I was recently nominated as “lecturer” at Sackler School of Medicine, Tel-Aviv University.

Today, I am still in touch with Dr. Olivieri... [and]... hoping that in future I will have the opportunity to join again to this fantastic group of people.”⁵⁰

Conclusion

The allegations by Drs. Berkovitch and Atanackovic were contradicted by documents and were not discussed in the reports of the Naimark Review or the MAC. Their allegations were, nevertheless, put forward to the MAC by Dr. O’Brodivich.

(9) The issue of REB involvement

The Board's conclusion that Dr. Olivieri had "failed" to inform the REB that a new risk had been identified, reiterated the conclusion to this effect in the Naimark Report. This conclusion is now documented to be incorrect (see sections 5K(7) and 5O), but the incorrect information which gave rise to this conclusion was repeated during the MAC inquiry. The MAC and its sub-committee relied on it, so we briefly summarize the relevant information in this section, to provide background for the next subsection, 5P(10).

The Board's directive to the MAC referred to two specific matters in which Dr. Olivieri allegedly failed to report the second risk of L1 she had identified, progression of liver fibrosis. These were in regard to: (i) the thalassemia patients who had continued on L1 under EDR; and (ii) the proposed study of L1 in treatment of sickle cell disease (SCD). However, the thalassemia patients were not in any research trial at the time in question, so the REB did not have any mandate. Its approval for any measures to monitor or treat thalassemia patients was not required. There were no patients in the proposed Sickle Cell Disease study, nor was there any intention of enrolling any patients for many months—the proposal was still under review by the REB and was not yet approved. The situation in regard to the thalassemia patients after the trials were terminated was discussed at some length in the Naimark Report, but that Report discussed the proposed SCD study only briefly (mainly in a paragraph starting on page 45, with brief mentions thereafter, in the Report's summary sections).

Some responsibility for the incorrect conclusions of the Naimark Review, and for the incorrect allegations the MAC publicly referred to external bodies, must be attributed to Dr. Moore, who became Chair of the REB shortly after Apotex terminated the trials. In response questions in late February 1997 and early June 1998 from Dr. O'Brodovich, she wrote that a trial "continued with full REB approval."⁵¹ As documented in section 5K(7), she was simply wrong. However, in late February 1997, Dr. O'Brodovich relied on her incorrect information to justify actions he had already taken during the preceding week, and he relied on it in making his allegations to the Naimark Review. The Review believed the incorrect statements by Dr. Moore and Dr. O'Brodovich that there had been a continuing trial.

In the MAC inquiry, both Dr. Koren and Dr. O'Brodovich cited and relied on Dr. Moore's June 1998 letter to Dr. O'Brodovich, in alleging that Dr. Olivieri had an obligation to report to the REB. Dr. Moore also gave testimony to the MAC in January 1999 in which she repeated the incorrect information she had provided to Dr. O'Brodovich in 1997 and 1998.⁵² The

importance of Dr. Moore’s misinformation was confirmed when legal counsel for the MAC wrote that the MAC had relied on her statements.⁵³

Under HSC policy and practice, an EDR treatment arrangement did not require REB approval. Dr. Koren had stated this in his *Textbook of Ethics in Pediatric Research*, published in 1993. He was knowledgeable on this topic, because he had just completed a term as Chair of the Human Subjects Review Committee (HSRC), the former name of the Research Ethics Board (REB). Chapter 17 is entitled, “The process of ethics review in pediatric research: the Toronto model.” At page 198, there appears:

Table 1. *Examples of studies which do not need approval of HSRC [REB] in Toronto*

1. Retrospective chart reviews.

.....

4. Compassionate use of an experimental drug [under the *EDR* program of Health Canada].⁵⁴ (italics in original)

In his book, Dr. Koren was clear and unequivocal on these two important points. In her written response to the MAC dated October 12, 1999, Dr. Olivieri included a photocopy of this page of Dr. Koren’s book.

Dr. Koren, with Dr. Olivieri, was a co-signatory to the LA-01 and LA-03 trial contracts, which gave Apotex the right to terminate the trials (see section 5A). He was the joint recipient with Dr. Olivieri of Apotex’s letter dated May 24, 1996 notifying them that it had terminated both trials (see section 5F). He also was present in Dean Aberman’s mediation meeting of June 7, 1996, in which the new, post-trial, EDR arrangement was set up, an arrangement that did not involve the REB. Dean Aberman recorded the names of those present, as well as the main outcome of mediation:

Although Apotex would not change their position on discontinuing the clinical trials, Apotex agreed to Emergency Drug Release (EDR) of L1 to any patient who was on L1 during the trial ...⁵⁵

In a number of letters written between May 1996 and May 1998, Dr. Koren confirmed that he knew *both* trials (LA-01 and LA-03) had been terminated. He was a co-signatory with Dr. Olivieri of letters stating this to Dr. Haslam and Dr. Zlotkin, dated May 25, 1996 and July 15, 1996, respectively. He wrote to Dr. Olivieri on August 15, 1997 and to Dr. O’Brodivich on November 3 and 26, 1997 concerning data of patients who had been in the LA-01 trial and in these letters confirmed that that trial had been terminated in May 1996. He wrote to Dr. Becker on April 15, 1998 and to Dr. Buchwald on May 14, 1998 concerning data of patients who had been in the LA-03 trial and in these letters confirmed that that trial had been terminated in May 1996.⁵⁶

In his written testimony to the MAC dated December 18, 1998, Dr. Koren did not state what he knew to be the case: that both trials had been

terminated. *Instead*, he put forward a quotation from Dr. Moore’s June 1998 letter to Dr. O’Brodivich, in which she stated incorrectly that a research trial continued after May 1996 under REB approval. He was in a position to correct the misinformation of Dr. Moore but he did not do so, and what is still more serious, he put forward “the views expressed in writing by Dr. Moore.”⁵⁷ *

Conclusions

1 | It is quite clear that in accordance with both HSC policy and practice, Dr. Olivieri was not required to seek REB approval to continue to treat and monitor patients receiving L1, after the trials were terminated in May 1996.

2 | Dr. Moore’s testimony was incorrect: there was no clinical trial of L1 in Toronto after May 1996 when both trials were terminated; and the REB had no jurisdiction over patients who were treated with L1 after May 1996 because they were in a non-trial EDR treatment arrangement. Both these facts are well documented in HSC records, including records available to Dr. Moore as REB Chair.

3 | Dr. Koren misinformed the MAC in this matter. He was the author of the book chapter describing the actual policy and practice at HSC. He was a participant in Dean Aberman’s mediation meeting that set up the new EDR arrangement that did not require REB involvement and did not have REB involvement. He wrote several letters during 1996–1998 confirming that both trials had been terminated. Yet he chose to repeat Dr. Moore’s information that he knew to be incorrect.

(10) The MAC “questions” & “concerns”

I. THE JANUARY 2000 MAC REPORT

The (undated) report of the *ad hoc* committee chaired by Dr. Roy was forwarded to Dr. Olivieri by MAC Chair Dr. Becker on January 18, 2000.⁵⁸ Dr. Becker’s covering letter repeated the “questions” in the report of the subcommittee and, for each “question,” expressed a “concern” that was in substance the same, thereby endorsing the report of the subcommittee—indeed the MAC’s report to the Board dated “April 2000” said:

*In his December 18, 1998 letter to the MAC, Dr. Koren included a quotation of the following passage from Dr. Moore’s June 3, 1998 letter to Dr. O’Brodivich: “When Apotex withdrew its sponsorship in May ’96, some patients (following detailed information session [sic] conducted by Dr. Olivieri) continued in the compassionate use trial [LA-03], but it was not regarded as a new trial and its REB approval was maintained.” (See sections 5H and 5K for references to documents and discussion of Dr. Moore’s erroneous view.)

The Medical Advisory Committee report was sent to Dr. Olivieri on January 18, 2000.⁵⁹

This collection of allegations, framed as “questions” and “concerns,” raised issues of possible specific misconduct by Dr. Olivieri.

To illustrate the subcommittee’s handling of the case, which was endorsed by the full MAC, we first consider question 5, concerning liver biopsies. The subcommittee’s report said that an issue regarding liver biopsies also underlay question 1.⁶⁰ More detailed information on liver biopsies and the MAC allegations concerning them is included in the following section, 5Q.

II. QUESTION 5

Question 5. “Did you schedule liver biopsies for patients receiving L1 in February, March, and April 1997? If so, Why?”

This question was in reference to biopsies of some patients that were scheduled following the identification (in early February 1997) of the risk of progression liver fibrosis in data on another group of patients (see section 5K). Following a brief review of the background and a brief review of Dr. Olivieri’s response on question 5, the subcommittee signified that her response was not accepted by stating:

The MAC may wish to consider whether these liver biopsies were secured for *research* purposes.”⁶¹ (emphasis added)

Dr. Becker, writing to Dr. Olivieri on behalf of the full MAC, stated:

The Medical Advisory Committee is concerned that the liver biopsies were secured for purposes of research.⁶²

The MAC *ad hoc* subcommittee apparently believed the incorrect allegations and testimony of Dr. Koren that liver biopsy was a risky procedure, and that these liver biopsies were done simply for research purposes, a view advanced also by Dr. O’Brodivich in his letter.⁶³ Dr. Koren testified that liver biopsy is a “potentially life threatening procedure” and that it was not clinically indicated in these cases. He did this even though he had in his possession documents establishing the incorrectness of his testimony. Dr. O’Brodivich put forward a misleading isolated quotation from a journal article in support of a position similar to Dr. Koren’s. (See section 5Q.)

The subcommittee summarized Dr. Olivieri’s response to question 5 as follows:

February 4, 1997, Dr. Olivieri and Dr. Cameron met with her patients in order to explain these findings. She also met with each of her patients individually to explain the problem, to ask them to undergo liver biopsy to determine whether liver damage had occurred and to advise patients and their families to discontinue L1 and return to conventional deferoxamine chelation therapy (page 38, Vol 1 Olivieri response to MAC).⁶⁴

This summary actually contains the essence of the matter:

the only way progression of liver fibrosis can be assessed is through comparative review of serial liver biopsy data; current biopsy data (histology and hepatic iron concentration) was needed to safely effect the transfer of patients to the standard therapy (deferroxamine).

However, the members of the subcommittee do not appear to have understood the information they were summarizing. Dr. Olivieri's submission documented that the situation in early 1997 was that a risk of progression of liver fibrosis from use of L1 had been identified in serial biopsy data of some patients who had been in the former LA-03 cohort. Therefore, it was medically necessary to assess other patients who had been on L1 and hence exposed to the risk, to determine whether any of them had experienced this serious adverse effect. These were mainly individuals from the former LA-01 cohort who had continued on L1. Since the only way progression of liver fibrosis can be determined is through histological examination of serial biopsy samples, new biopsy data was clinically required to determine whether LA-01 patients had been adversely affected, and so whether and how their management needed to be changed.

Had MAC members diligently reviewed Dr. Olivieri's submission and reviewed the medical literature cited in it,⁶⁵ or consulted independent experts, they would have discovered that liver biopsy is a safe procedure that is necessary for proper management of the care of transfusion-dependent thalassemia patients, regardless of whether they are on standard or experimental iron-chelation treatment, and regardless of whether or not they are in a research trial. Biopsy data is needed for assessing the effectiveness of chelation so dosage schedules can be adjusted, as well as for assessing safety through histology.

The report of the *ad hoc* subcommittee says that a member reviewed the charts of the patients concerned:⁶⁶

The charts of the patients in question were reviewed by the subcommittee and indeed, liver biopsies were undertaken. In every instance a consent was secured for liver biopsy done under ultrasound sedation [sic] and /or general anaesthesia. *No reference was made to an ongoing research project.*⁶⁷ (emphasis added)

The reason there was no reference to "an ongoing research project," of course, is that from late May 1996 onward there *was none*. The EDR therapeutic use of L1 was not under REB jurisdiction, and the patients had these tests because they were clinically indicated and necessary to manage their care. (See sections 5G, 5H, 5K and 5Q.) It is unfortunate that no member of the MAC appears to have reviewed a wider sample of charts of thalassemia patients, including charts of some who were on standard

therapy. Had they done so, they might then have appreciated that liver biopsy was a standard diagnostic procedure for patients at risk of liver damage and the only means of assessing progression of liver fibrosis.

Since the summary of Dr. Olivieri's submission quoted above refers only to the covering brief in Volume I of her three-volume response, it is possible that the members of the subcommittee did not read the information provided on this question in the supporting documents. If they did read it, then either they did not comprehend it, or they arbitrarily gave more weight to the non-expert testimony of Dr. Koren and Dr. O'Brodovich. However, the testimony provided by Drs. Koren and O'Brodovich was wrong to such an extent that the subcommittee should have been alerted to critically examine their allegations and testimony on other topics.

Conclusion

In her written response to the MAC of October 12, 1999 Dr. Olivieri explained that she scheduled liver biopsies for patients because they were clinically indicated, and she gave the reasons with reference to the medical literature. The subcommittee and the MAC should have accepted her response, or consulted independent experts. They did neither, and instead appear to have believed the incorrect testimony of two witnesses who were not experts, Drs. Koren and O'Brodovich.

III. DENIAL OF DUE PROCESS

It is a matter of importance that question 5, as posed to Dr. Olivieri, conveyed no direct suggestion that allegations of improper use of biopsies lay behind it. The question was simply, "Did you schedule biopsies...? If so, why?" Dr. Olivieri provided a full response⁶⁸ to that question as it was posed to her—namely that these biopsies were clinically indicated and the reasons—but she could not have reasonably anticipated that there was a specific allegation of misconduct lying behind the question. Had the allegations and testimony on this matter been disclosed to her, she could have easily highlighted sections of her response to the MAC, to guard against any possible misunderstanding by MAC members.

IV. QUESTION 1

Question 1. "When did individuals receiving L1 in the LAO3 Trial cease to be 'subjects of research'? When did individuals receiving L1 in the LAO1 Trial cease to be 'subjects of research'?"

As reasons for not accepting Dr. Olivieri's (October 1999) response, the MAC subcommittee cited Dr. Olivieri's 1997 ASH abstract (see below), and her remarks at the December 1996 ASH meeting about the need to review historical biopsy data in charts.⁶⁹ The subcommittee added:

The MAC may wish to consider whether the results being derived from the liver biopsies in the long-term cohort indicated that the study was ongoing.⁷⁰

The full MAC repeated question 1 and said it was:

concerned that patients were subjects of research in both the LA01 and LA03 trial beyond the date of October 31, 1996.^{71*}

These statements, one by the subcommittee and the other by the MAC, together make two distinct allegations: (i) that chart review constituted unauthorized research; and (ii) that standard clinical monitoring of transfusion-dependent thalassemia patients constituted unauthorized research. Both are incorrect, as noted in sections 5P(9) and 5Q. Here we review the testimony cited by the MAC as supporting these allegations.

Dr. Olivieri's remarks at the December 1996 ASH meeting are discussed in section 5K—they had nothing to do with any patients being subjects of unauthorized research. Reviewing historical biopsy data in charts to determine whether patients had experienced an unexpected adverse reaction over a period of several years did not mean that the patients were subjects of unauthorized research. Once she learned (in early December 1996) that an iron chelator chemically similar to L1 had been shown to cause progression of liver fibrosis in an animal model, it would have been unethical and irresponsible for Dr. Olivieri not to have reviewed the historical biopsy charts of patients who had been in the long term (LA-03) cohort, assessed the results, drawn conclusions and taken clinically indicated action to assess other patients in her care who had been on L1 for this adverse effect (see above re: MAC question 5). It was then also important to inform physicians administering L1 in other centres of this risk, through publication of the results of the chart review. Chart review and publication of findings from it did not require REB approval and did not constitute unauthorized research (see section 5P(9)).

Legal counsel for the MAC listed several documents as constituting evidence “which suggests the LAO1 and LAO3 trials were not terminated in 1996.”⁷² These were: (i) letters by Dr. Moore to Dr. O’Brodivich dated June

*The MAC’s reference to “October 31, 1996” arose because it did not detect an error in the (undated) report of its subcommittee. In that report, at page 3, the content of a short paragraph at pages 32–33 of Dr. Olivieri’s October 1999 brief was misrepresented. What Dr. Olivieri actually wrote was that the trials were terminated on May 24, 1996 and, “Therefore, the REB responsibility for these clinical drug trials also ceased on that day.” October 31 was the date by which the post-termination “closeout” work (required by the protocols) was completed, as Dr. Olivieri clearly stated.

3, 1998 and February 27, 1997; (ii) the 1997 ASH abstract by Drs. Olivieri and Brittenham (incorrectly dated by the subcommittee and by MAC counsel as 1998); and (iii) testimony of Ms. Naomi Klein that L1 had been “given to patients in the studies until May 1997.”⁷³ These will be dealt with in turn.

(i) As discussed in subsections 5K(7) and 5P(9), Dr. Moore’s statements in her letters to Dr. O’Brodivich dated June 3, 1998 and February 27, 1997, that one trial (specifically, LA-03) continued after May 1996, were incorrect. Both the LA-01 and LA-03 trials were terminated in May 1996, neither was continued or reinstated, and no new trial of L1 began.

(ii) Dr. Olivieri and Dr. Brittenham were co-authors of an abstract presented at the December 1997 ASH meeting, reporting data on hepatic iron concentrations (HIC) of some of the patients who had been enrolled in the randomized trial (LA-01). This trial, as well as the long-term trial (LA-03), had been terminated in May 1996. The HIC data reported in the abstracts was in the clinic charts of patients. At the Hospital for Sick Children chart review studies did not require REB approval, so Dr. Olivieri’s reporting of chart review data in the 1997 ASH abstract did not imply that the patients were “subjects of research,” and such publication did not require REB approval (see section 5P(9)).⁷⁴

Counsel for the MAC also quoted as a basis for MAC “concern” a sentence from the 1997 ASH abstract, “In Toronto, hepatic iron concentration determined by biopsy or magnetic susceptometry (SQUID) was monitored until May 1997, when L1 was discontinued because of safety concerns.”⁷⁵ This sentence had been quoted by the MAC subcommittee, which added, “...the MAC may wish to consider whether the REB should have been advised of these findings described in the abstract.”⁷⁶

A copy this abstract had been provided by Dr. Koren to Dr. O’Brodivich, who made an allegation to Dr. Naimark on the basis of it.⁷⁷ In their letters to the MAC, Drs. Koren and O’Brodivich both alleged that this abstract provided evidence that Dr. Olivieri continued to administer L1 to HSC patients after February 1997—the same allegation Dr. O’Brodivich had made to Dr. Naimark. Neither this nor any other of their allegations to the MAC were disclosed to Dr. Olivieri, so she did not address this abstract in her October 1999 submission to the REB.

The facts are as follows. Dr. Olivieri had successfully counselled all patients in HSC to interrupt use of L1 in February, pending results of liver biopsies. These patients did not subsequently resume its use, as was clearly documented in Dr. Olivieri’s October 1999 response to the MAC.⁷⁸ A few adult patients in The Toronto Hospital refused to stop immediately, and one or two continued until May, but they did so in the full knowledge of the newly identified risk. Although the HSC patients stopped using L1 in

February, the liver biopsies for this group were not completed until April, as the MAC noted. Analysis of the results was not completed until May. The reference to May in the abstract did not mean that any HSC patients were on L1 until May, contrary to the allegation of Dr. Koren and Dr. O’Brodivich.

Because the patients had not been in a research trial since May 1996, there was no requirement to advise the REB. However, after February 1997, because Dr. O’Brodivich had strongly insisted Dr. Olivieri inform the REB, she continued to inform Dr. Moore about the results of the biopsies and care management decisions made in light of the results,⁷⁹ although there was no requirement in policy for this. As already noted, HSC policy also did not require REB approval for publication of research based on chart reviews.

(iii) Testimony of Ms. Klein was put forward to the Naimark Review three times by Drs. Koren and O’Brodivich, working in collaboration. In the first of her letters, she stated that both trials continued until May 1997.⁸⁰ In the second, she stated that patients continued on L1 at both HSC and TTH until the end of May 1997.⁸¹ This testimony is documented to be incorrect, as noted above. Also, Ms. Klein had herself been included in 1996 correspondence wherein it was clearly stated that the patients were no longer enrolled in any trial after May 1996.⁸² However, at the time she wrote the three letters (two to Dr. Koren, one to Dr. O’Brodivich), Ms. Klein was not in Toronto and did not have access to the records; her memory did not serve her well. In her third letter, she backed off from her earlier assertions, saying that these were “to the best of [her] recollection,” since she did “not have any documentation” to review.⁸³

Conclusion

There is no basis to the MAC “concern” that patients in the former trial cohorts were “subjects of research.” The trials were terminated on May 24, 1996 and Dr. Olivieri’s subsequent medical actions were clinically indicated, involved procedures well established in the literature, and were in accordance with EDR regulations and clinical ethics. Her publication of data based on chart review did not require REB approval and it was important for physicians treating thalassemia patients in other centres to know of the results of this chart review.

V. QUESTION 2

Question 2. “When did you report your conclusions regarding the toxicity of L1:

a) to the Research Ethics Board;

- b) to patients and parents using L1;*
- c) and to colleagues prescribing L1?"*

Question 2a). The accompanying “concern” was that, “Members of the Medical Advisory Committee are concerned that you should have reported your conclusions with respect to L1 toxicity to the Research Ethics Board.” This “concern” arose from allegations by Dr. Koren and Dr. O’Brodivich, and incorrect information from Dr. Moore, and the consequent erroneous finding in the Naimark Report. Not only was there no requirement to report to the REB, Dr. Olivieri was under legal warnings from Apotex not to inform anyone. In consequence, she informed those she was ethically and legally obligated to inform, patients (or their parents or guardians), and those she was legally required to inform, Apotex and the regulatory agencies. She informed the REB after Dr. O’Brodivich insisted she do so, but he had no basis in policy or practice for this. Indeed, it was not until a week after Dr. O’Brodivich insisted the REB be involved that he wrote to Dr. Moore to ask if the REB had any mandate in this circumstance, and received Dr. Moore’s incorrect answer. (See sections 5K(7–8) for details and citations.)

Conclusion

The REB had been duly notified in 1996 that both L1 trials were terminated. Patients who continued on L1 were not in a trial, the REB had no jurisdiction, and there was no requirement to inform the REB of any development concerning these patients.

Question 2b). “*When did you report your conclusions regarding the toxicity of L1 to patients and parents using L1?*” Volume 1 of Dr. Olivieri’s response to the MAC “questions” included a statement by Dr. Cameron, the liver pathologist whose analysis of serial biopsy slides of patients from the former long-term trial cohort resulted in the identification of the risk of progression of liver fibrosis. Dr. Olivieri had been reviewing the data and their significance with Dr. Brittenham and Dr. Cameron from late December 1996 onward, and by January 22, 1997, they had come to a tentative finding and prepared a draft report to the regulatory agencies. In his statement, Dr. Cameron described subsequent events:

I asked Dr. Olivieri to delay finalizing this report because I wished to re-assess the slides and my scores.... Thereafter, I completed a detailed review of all the biopsies. I also compared my observations with the original pathologists’ reports. My original observations were verified. This review was finalized in early February and I reported my conclusions to Dr. Olivieri. I met with the patients in the L1 trial on February 4, 1997 to provide them with my findings.⁸⁴

In addition to Dr. Olivieri and Dr. Cameron, Dr. Melanie Kirby (the clinic physician in The Toronto Hospital (TTH)), and the social worker for the program were also present in this first (February 4) group meeting with patients.⁸⁵ Dr. Olivieri thereafter personally discussed the new risk with all 14 HSC patients on L1 and their families. All adult patients were personally contacted by either Dr. Olivieri or Dr. Kirby. She also held an additional group information meeting for patients and parents on March 6.⁸⁶ (See section 5K.)

The MAC *ad hoc* subcommittee and the full MAC accepted Dr. Olivieri's answer to this question.

Question 2c). "When did you report your conclusions regarding the toxicity of L1 to colleagues prescribing L1?" The MAC appended a "concern" to the question of when Dr. Olivieri reported her conclusions regarding the toxicity of L1 to colleagues prescribing it, "Members of the Medical Advisory Committee are concerned that you should have advised your Department Chief and your co-workers of your concerns about L1 toxicity."⁸⁷

This question and concern appear to have arisen from allegations and testimony by Dr. O'Brodovich and Dr. Koren. In Dr. O'Brodovich's written testimony to the Naimark Review, he stated that the assisting physician in the HSC thalassemia clinic, Dr. Massicotte, "had not been informed" of the risk of progression of liver fibrosis until he himself informed her on February 19, 1997, while in his letter to the MAC he implied this but did not state it directly.⁸⁸ He also suggested to the MAC that Dr. Olivieri was obligated to inform him. Dr. Koren alleged to the Naimark Review and to the MAC that Dr. Olivieri had not informed him of this risk.⁸⁹

In addition to Dr. Olivieri herself, the colleagues prescribing L1 were the assisting physicians, Dr. Kirby in the TTH clinic and Dr. Patricia Massicotte in the HSC clinic. Dr. Olivieri reported to us that she informed them in late January 1997 of her concern that there may be a risk of progression of liver fibrosis, while Dr. Cameron was checking his analysis of the liver biopsy slides. She said she directed the clinic physicians to counsel any patients who came into the clinics for their regular blood transfusion or other treatment during this period, to agree to have an early (in advance of their annual date) liver biopsy scheduled, if they had not recently had one. The patients who came in for this purpose before the February 4 group information meeting were advised that there was an unspecified "suspected problem," and that the early biopsy was a matter of precaution.⁹⁰

This Committee of Inquiry was provided with copies of HSC clinic records for several thalassemia patients who were on L1 under EDR (with patient identifiers removed) showing that Dr. Massicotte herself scheduled

several of the early biopsies. Her signature is on the relevant forms, on each of which is the date of the patient’s last biopsy and a notation to the effect that the patient should consider having a biopsy “soon,” or “next visit.” It is clear that these biopsies were being scheduled well in advance of the annual date. Two of these forms signed by Dr. Massicotte are dated in late January (28 and 31), the others in the first half of February.

In regard to the information meeting for patients held on February 4, Dr. Olivieri reported to us that the nurses, the social worker, and Dr. Massicotte all were fully informed of this meeting in advance, and of its purpose: to explain the newly identified risk to patients. She reported that this meeting was held at 7:30 PM on February 4 but Dr. Massicotte did not attend, as her usual time of departure was 4:30 PM to drive back to Hamilton where she was living and working part-time with Dr. O’Brodivich’s wife. Although she had not attended it, Dr. Massicotte herself confirmed to the MAC subcommittee that she knew the meeting had been scheduled.⁹¹

Dr. O’Brodivich, Dr. Olivieri’s Department Chief in HSC, was not advised by her until after Apotex contacted him, and he then contacted her. However, she was under no obligation to advise him. She had the situation well in hand medically, was the medical expert in this area, and her assisting physicians Dr. Kirby and Dr. Massicotte had been informed in a timely manner. In late January, Dr. Olivieri had consulted with Dr. Baker, Physician-in-Chief in TTH, whose specialty, hematology, was much more closely related to the medical situation than Dr. O’Brodivich’s specialty.⁹² All but one of the patients in the group at greater risk (those in the former long-term trial cohort) received their care in TTH—this was the group in whose serial biopsy data the risk was identified. In his letter to the MAC, Dr. O’Brodivich indicated displeasure that Dr. Olivieri had consulted with Dr. Baker, but not with him.⁹³ However, Dr. O’Brodivich, by his own written account, does not have the relevant expertise, so would not have been able to offer medical advice.⁹⁴

Dr. Koren’s allegations and testimony that he had not been informed of the risk were untrue. Dr. Olivieri sent him the full report on the newly identified risk on February 5, 1997 and he admitted to HSC’s harassment investigator Ms. Humphrey that he received the copy Dr. Olivieri sent him “in early February 1997.”⁹⁵ (See below and sections 5K, 5O and 5R.)

Conclusion

Underlying questions 2 a), b) and c), all related to when, and to whom, Dr. Olivieri reported her identification of the second risk of L1, was an allegation that patient safety was compromised. This was not the case. Patients and their families were advised of the new risk in a group meeting

immediately upon its confirmation by Dr. Cameron, and the medical circumstances were explained to them individually during the next two weeks. There was no requirement to inform the REB, but when it was in fact informed, this had no effect on patient care (see section 5K). The documentary evidence is that all physicians and other professional staff in the thalassemia clinics were informed immediately, and so also was Dr. Koren. There was no obligation in policy or practice to inform Dr. O’Brodovich; also he did not have the relevant expertise, so there would have been no purpose in consulting him informally. In summary, there is no basis for the MAC allegations (cast as “concerns”) pertaining to any part of question 2.

VI. CONTRADICTIONS IN DR. KOREN’S TESTIMONY

Dr. Koren alleged both to the Naimark Review and the MAC subcommittee that Dr. Olivieri’s discussion at the December 1996 ASH meeting was proof that she had by then identified a risk of L1. He alleged: “Sometime in the Fall of 1996 Dr. Olivieri began to suspect that L1 causes severe liver toxicity, and more specifically—liver fibrosis,” and that she had presented “findings” to this effect at the ASH meeting. He further alleged that she had failed to inform the relevant authorities, among which he numbered himself, of her purported findings.⁹⁶

In fact, two months later, in early February 1997, when Dr. Olivieri actually had confirmation of probable causality between L1 and progression of liver fibrosis in the data on some patients, she reported it to Apotex and HPB, as well as to patients in her care who were on L1 and her assisting physicians in the clinics. If she had reported on the basis of an uninvestigated “suspicion” from an animal study, she would have been at further risk of legal action by Apotex for reckless damage to the commercial viability of their drug, a point Apotex made repeatedly to her, in writing. (See section 5I.)

Although she was not obligated to do so, Dr. Olivieri did inform Dr. Koren of this risk in writing on February 5, 1997, directly after it was scientifically identified in early February. Through their joint CMPA counsel, Mr. Colangelo, she sent him a copy of the full report she and Drs. Brittenham and Cameron had prepared for the regulatory agencies.⁹⁷ Dr. Koren did not acknowledge to the MAC that he had received this report from Dr. Olivieri. The summary of his oral testimony to the MAC of January 19, 1999 records that, “He stated that he was not advised of toxicity concerns.”⁹⁸ Mr. Colangelo’s covering letter to Dr. Koren and the report were included in Dr. Olivieri’s response to the MAC, yet the MAC apparently did not invite Dr.

Koren back to explain this conflict between his testimony to them and the documentary record. Later in 1999 Dr. Koren acknowledged to the Hospital's investigator, Ms. Humphrey, that he had in fact received the copy of Dr. Olivieri's report that she sent to him through Mr. Colangelo, shortly after it was sent "in early February 1997." In view of these facts, we conclude that Dr. Koren was not truthful to the MAC on the matter of being advised of the risk by Dr. Olivieri.

In his letter and testimony to the MAC, Dr. Koren attempted to bolster his incorrect allegations that he was not informed of the risk by a claim that he had formal medical responsibility for the patients, and so should have been informed. It is a matter of record that he had neither the responsibility, nor the relevant expertise. On the first, second and fourth pages of his letter to the MAC, Dr. Koren asserted that he was the person in the role of 'the practitioner' in the sense of the *Food and Drugs Act and Regulations*, for purposes of the EDR treatment of patients with L1. He wrote, "I was... the individual responsible for Emergency Drug Release" and that, in the event of an adverse drug reaction, he therefore was the person to report this result "to the company and to the government, according to Health Canada regulations."⁹⁹ The summary of his testimony shows that he repeated this when he met with the MAC a month later, asserting that he "had been the compassionate release drug (EDR) signing physician" (i.e., 'the practitioner').¹⁰⁰

However, both Apotex and the Health Protection Branch (HPB) of Health Canada understood Dr. Olivieri, the treating physician of the patients, to be 'the practitioner.' This understanding is documented and it was she who was authorized by HPB to prescribe the drug, required to monitor the patients, and report on the results of the treatment to Apotex and HPB.¹⁰¹ Under the arrangement mediated by Dean Aberman on June 7, 1996 and again on November 14, 1996, Dr. Koren was, in effect, designated as a pharmaceutical courier who received the drug from Apotex and deposited it with the Hospital pharmacy. This arrangement was made because "the working relationship between Dr. Nancy Olivieri and Apotex has not been mutually satisfactory."¹⁰² There was no suggestion that he would be the treating physician of thalassemia patients, since he is not qualified in the relevant medical disciplines. Furthermore, in several letters he wrote in 1997 and 1998 he stated he had no responsibility for, or involvement with, patients after the trials were terminated in May 1996.¹⁰³ Although Dr. Koren's claim was contradicted by the documentary record, his claim was endorsed by Dr. O'Brodovich in testimony to the MAC.¹⁰⁴

Dr. Koren contradicted himself in his letter to the MAC as well. On the fifth page, Dr. Koren wrote, "Dr. Olivieri refused to give Apotex immediate details about her suspicions and proofs of serious (liver) toxicity, despite clear

regulations by Health Canada.”¹⁰⁵ In other words, she, not he, was ‘the practitioner’ who was required to report adverse reactions to Apotex, as well as to HPB. We have no evidence that the MAC questioned this or any other inconsistency in his information.

Conclusions

1 | Dr. Koren claimed that he knew of the risk of progression of liver fibrosis as early as “December 18, 1996”^{*} and also that *he* was the person who had the obligation to report it to the relevant authorities, among which he included the REB. Although this was apparently accepted by the MAC, it must be noted that Dr. Koren himself made no such report and therefore he too “failed,” in the same sense the Board had concluded in regard to Dr. Olivieri. Yet the MAC did not investigate his “failure.”

2 | Dr. Koren was untruthful with the MAC. His testimony on identification of the risk and the reporting of it was contradicted by documents available to the MAC, yet we have seen no evidence that the MAC pursued the inconsistencies in his information, or were alerted to question his other information.

^{*}See Dr. Koren’s letter purportedly dated “December 18, 1996” reproduced at page 41 of the Naimark Report, and his letter of December 18, 1998 to Dr. Roy, for his usage of the date “December 18, 1996.” In these letters he cites Dr. Lishner of Tel Aviv University and Dr. Spino of Apotex as his sources of information.

VII. QUESTION 3

Question 3. “Did you continue to prescribe L1 after you concluded it was toxic. If so, why?”

To this was added:

Members of the Medical Advisory Committee are concerned that documents indicate that you continued to administer L1 after you advised the FDA of your concerns.”¹⁰⁶

This wording was later amended to read:

Members of the Medical Advisory Committee are concerned that documents indicate that Dr. Olivieri continued to administer L1 to her patients after drafting a letter to the FDA on January 22nd, 1997.”¹⁰⁷

That there could be any “concern” on this matter after study of Dr. Olivieri’s thorough response is surprising. Dr. Olivieri’s submission documented the fact that this risk was one of chronic, not acute, toxicity. The circumstance Dr. Olivieri and the patients had to contend with in early February 1997 was one of balancing two chronic risks: the long established risk of chronic toxicity of iron-loading from transfusions in the absence of chelation, as against the newly identified risk of chronic toxicity of the chelator L1. Patients with thalassemia major are regularly counselled from early childhood of the dangers of iron-loading and the importance of chelation therapy to reduce tissue iron concentrations. They had agreed to be administered the unproven drug L1 because of the onerous nature of the standard therapy (subcutaneous infusion of deferoxamine) and were disinclined to return to it, because it was so onerous.

As outlined above and in section 5K, following the first group information meeting on February 4, Dr. Olivieri met individually with each of the HSC patients on L1 and their parents, and she or her assistant Dr. Kirby met with each of the TTH patients. In these meetings she reviewed the new findings and the competing risks. She recommended that all those who had not had recent liver biopsies should have one in the near future. She counselled all patients to interrupt* L1 until the results of the liver biopsies were known, as this information would be needed to determine future therapy for each, as well as to determine whether they had experienced progression of liver fibrosis. In the two weeks following the February 4 meeting, while these individual meetings were being held, some patients were provided with new L1 prescriptions on the basis that acutely stopping L1 might present a greater risk, particularly in patients whose tissue iron concentrations had been in a high range when last

*Short-term interruption of chelation is not considered to pose a risk, but the safety margin in time may depend on the level of the patient’s hepatic iron concentration.

measured.* However, on or before February 20, all HSC patients and their parents had agreed to interrupt use of the drug, and no prescriptions for L1 were filled by the HSC pharmacy after February 18.¹⁰⁸ As well as providing each patient with full information on her/his own health status, Dr. Olivieri counselled them that best course of action was to transfer to standard therapy.¹⁰⁹ This is not a simple matter and takes time. Proper administration of deferoxamine requires knowledge of the patient's current hepatic iron concentration and liver histology, in order to determine when to start and the dosage level needed.¹¹⁰

It is of note that, at the time of their MAC submissions, there is evidence in their own documents that neither of Drs. Koren and O'Brodovich believed that there had been a risk to patients in early 1997,¹¹¹ yet they wrote and said the opposite to the MAC. Also, at the time in 1997, Dr. Olivieri invited Dr. O'Brodovich to consult experts in the field of thalassemia, if he had any concerns about her management of patient care, but we have seen no record that he did so.

Conclusion

There is no basis for the MAC "concern" that Dr. Olivieri continued to prescribe L1 after she had identified a risk that it may cause progression of liver fibrosis. Dr. Olivieri immediately informed patients and explained that this new risk was chronic, not acute, and explained the resulting change in the balance between risks and benefits. She successfully counselled all HSC patients to interrupt L1 use, and effected their transfer to standard therapy in a safe and orderly way.

VIII. QUESTION 4

Question 4. "Did your application (January 1997) to the Research Ethics Board for approval of the study 'to examine the effects of L1 in patients with sickle cell disease' include information about risk of hepatic damage or cirrhosis associated with the administration of L1?"

To this question the MAC added:

Members of the MAC are concerned that you should have included your concerns regarding the L1 toxicity in your application to the Research Ethics Board.

*Some patients had been without L1 chelation for periods of time during late 1996 and early 1997 because Apotex had stopped supplying the drug, and had not immediately reinstated it, despite a second intervention by Dean Aberman on November 1996. This had been a concern to patients and their parents, and to Dr. Olivieri, as correspondence from the time shows (see section 5J (3)).

The facts were straightforward and clearly explained by Dr. Olivieri in her October 1999 submission to the MAC, yet her answer was not accepted.

Counsel for the MAC characterized the MAC report as embodying “patient care concerns.”¹¹² However, this application to the REB actually concerned a *proposed* clinical trial, many months away from the beginning of enrolment of patients. Dr. Olivieri had submitted the application in August 1996, well before the risk of progression of liver fibrosis was suspected. It made its way through the approval process over the subsequent months, including review by a referee and signed approval by the Department Head. Dr. O’Brodivich’s signature as Head bears the date of January 22, 1997.¹¹³

Dr. Cameron finalized his review of serial biopsy slides in early February 1997 and only then was he prepared to confirm that there was a risk and co-sign the letter to the regulators. Dr. Olivieri reported to us that her first priority at that juncture was to discuss this finding with patients on L1 and counsel them to interrupt use of the drug in the short run, pending results of liver biopsies. She also had to spend time with lawyers dealing with the additional legal warnings from Apotex to deter her from informing anyone, including patients, of this risk of chronic toxicity. Revising an application form for a study that was not to begin for many months was, reasonably, not a priority. She did not then have time to make any serious preparations for starting any new study. In addition, the risk from the sister drug of L1 seen in animal studies had occurred only in the iron loaded animals, and the proposed SCD study specifically excluded any patient with tissue iron loading from participating.¹¹⁴

When Dr. O’Brodivich raised concerns with Dr. Moore later in February about the sickle cell disease (SCD) study and Dr. Moore contacted her, Dr. Olivieri promptly provided full information,¹¹⁵ even though she was under Apotex legal warnings to deter her from discussing anything adverse about L1 with anyone. Dr. Olivieri agreed to submit revised information and consent forms for the proposed SCD study to the REB for approval, and Dr. Moore replied on February 24, signifying her agreement with this course of action.¹¹⁶ Dr. O’Brodivich, who on February 19 had insisted on involving the REB in monitoring Dr. Olivieri’s work, decided on February 26 to “withdraw [his] approval of this application.”¹¹⁷

The REB discussed the proposed SCD study during its meeting of February 14, 1997. The minutes record that the REB “suggest[ed] that it be conducted on an adult population prior to children” (because of the onerous nature of the protocol requirements) and requested more information. Further, “The Board... requests revisions to consent forms concerning clarification on... all possible drug side effects.”¹¹⁸ Thus: (i) in the view of the REB on the 14th of February, the commencement of this trial with actual

patients was not imminent; (ii) the REB was going to ask Dr. Olivieri if there were any newly discovered risks (which Dr. Moore did on the 20th and Dr. Olivieri explained the new risk in a reply letter that same day); and (iii) the REB suggested the trial commence with adults (hence no patients in HSC). On learning of this last point, Dr. Olivieri then gave active consideration to commencing with adults only, in TTH. She consequently considered applying for ethics approval in that hospital, and transferring the requested NIH grant there.¹¹⁹ Dr. O’Brodoovich reviewed the status of this study proposal with Dr. Moore on February 19 or 20 (she then contacted Dr. Olivieri on February 20—see section 5K for citations), so it is possible he was briefed on the REB discussion of February 14.

Differences between SCD and thalassemia were outlined in Dr. Olivieri’s submission to the MAC.¹²⁰ Patients with SCD are not typically transfusion-dependent and so are not typically at risk from chronic iron loading of organ tissues. Rather, red cell membranes in patients with SCD carry abnormal deposits of free iron. The iron induces damage to the cell walls, resulting in cell destruction and severe anemia. Importantly, the standard chelator for removing iron from other organ tissues, deferoxamine, does not work to remove iron from membranes of red blood cells. In 1995, Dr. Robert Hebbel (University of Minnesota) had shown that L1 could be useful in removing iron from red blood cell membranes, *in vitro* and *in vivo*. Following the publication of that study, Drs. Olivieri, Brittenham, Hebbel and Elliot Vichinsky (Oakland) sent an application to the NIH for funding for a short-term, multi-centre clinical trial.¹²¹ An objective of this proposed trial was to be determination of “the efficacy of L1 in improving red cell membrane abnormalities... and extending red cell survival.”¹²²

The study in an animal model of the iron chelator chemically similar to L1 had determined that the chelator *by itself* did not induce fibrosis. All animals in the study that showed evidence of progression of liver fibrosis had been administered both iron and the chelator. Even though in animals not iron-loaded that chelator showed no adverse effect, this did not prove that L1 alone could not cause fibrosis in humans who were not iron-loaded. On this account, the investigators decided in February 1997 to delay further the start of the proposed SCD trial “until the issue of deferiprone toxicity was more clearly defined,” and they so informed the program officer of NIH (the proposed funding agency in this case).¹²³

Finally, in December 1997, Dr. Moore wrote in response to an inquiry that the matter of the SCD study proposal had been satisfactorily dealt with through discussions and correspondence between her and Dr. Olivieri in the period February—April 1997.¹²⁴ Unlike Dr. Moore, the members of the MAC do not appear to have sufficiently appreciated some critical medical

differences between thalassemia and sickle cell disease (SCD), or the fact that the SCD study was a proposal (not an actual study), despite the fact that this information was provided to them in Dr. Olivieri's written submission.

Conclusion

The MAC and its subcommittee had no reasonable basis not to have accepted Dr. Olivieri's answer to question 4, and should have accepted it.

(11) Failure to provide due process

On January 11, 1999, a month after the MAC inquiry had been initiated by the Board of Trustees, Ms. Beth Symes, counsel for Dr. Olivieri, wrote to Mr. David Stockwood, counsel for the MAC, expressing concerns that:

the Hospital is actively pursuing a range of issues against Dr. Olivieri both at the MAC, within HSC and in public.¹²⁵

Among these issues Ms. Symes listed the two actions taken on January 6, 1999: the summary removal of Dr. Olivieri from her program directorship; and the letter directing her not to criticize the Hospital publicly (see section 5M). Ms. Symes added that the letter informing Dr. Olivieri of her removal from the directorship "was given by the Hospital to the National Post."¹²⁶

In her January 1999 letter to Mr. Stockwood, Ms. Symes referred to discussions they had had in December 1998, from which she had gained the impression that "issues of when had concerns about L1 arisen and to whom and when they had been conveyed" could be resolved through a review of the existing collection of "letters and memos between the parties." She said that in light of the recent actions against Dr. Olivieri by the Hospital, "it is our position that the process being used in carrying out the Trustee's [sic] direction must change."¹²⁷ Ms. Symes continued:

Dr. Olivieri is prepared to cooperate fully with the investigation by the sub-group of the MAC. Because of the nature of the allegations and the possible consequences to her medical career, she is entitled to know the specifics of the allegations, which are being made against her.

We propose that the persons who are making the allegations against Dr. Olivieri set out their concerns in writing and provide copies of the documents upon which they rely. Dr. Olivieri will then review these statements and prepare a detailed written response.¹²⁸

This request was not granted. Instead, Dr. Olivieri was provided only with the letter dated February 16, 1999 from Dr. Roy, Chair of the MAC *ad hoc* subcommittee, in which he listed the five questions and requested a written response. Subsequently, on October 12, 1999, on the advice of counsel, Dr. Olivieri submitted her written response to the five questions,

without knowing the underlying allegations and testimony against her, as discussed earlier in this section.

In his letter of January 18, 2000, Dr. Becker requested that Dr. Olivieri appear before the MAC “to respond to the above issues [the five ‘questions’ and ‘concerns’].” He added, “legal counsel will not be present during the discussion,”¹²⁹ and gave the following basis for denying Dr. Olivieri the opportunity to be represented by counsel during the actual hearing:

As you know the Medical Advisory Committee is not a tribunal. Its function is purely advisory.¹³⁰

We consider that, in the circumstances, this was not a reasonable basis for denying legal representation. It is technically correct that the MAC is purely advisory, but it was improbable that the Board of Trustees would not have acted to approve a recommendation by the MAC in this matter. Dr. Olivieri had been accused of misconduct by the Hospital’s Pediatrician-in-Chief Dr. O’Brodivich in the Naimark Review (as well as in the MAC inquiry), the Board’s December 1998 resolution asserted that she had committed misconduct (a “failure” to report), and the MAC is the body upon which the Board depends for advice on disciplinary action against medical staff. In addition, there is no grievance and arbitration procedure available to HSC medical staff that would provide a fair appeal mechanism against a recommendation of the MAC, a decision by the Board, or any other significant action adversely affecting their employment status. It was clear from the report of the *ad hoc* subcommittee that allegations had been accepted that had not been disclosed to Dr. Olivieri, despite the express written assurance by Dr. Roy in December 1998 that such would be disclosed if considered by the committee,¹³¹ and despite the written request by counsel Symes in January 1999 for disclosure. It was also clear from the subcommittee’s report and its endorsement by the MAC that the allegations had been given credence on the basis of incorrect testimony—testimony that was contradicted by well-documented medical and other information in Dr. Olivieri’s October 1999 submission. Representation by legal counsel in the meeting with the MAC should have been permitted, by any reasonable standard of fairness.

Around the beginning of February 2000, the University of Toronto Faculty Association (UTFA) decided to provide assistance to Dr. Olivieri in the matter of the MAC inquiry, in addition to assistance it was providing to her in other matters. The result was that her legal representation in HSC matters was assumed by lawyers from the firm of Sack, Goldblatt and Mitchell, from then onward. Over the next month, Dr. Olivieri and her new legal counsel Ms. Cathy Lace made repeated requests for disclosure of the allegations and testimony considered by the *ad hoc* subcommittee.

Finally, on March 10, 2000, MAC counsel Ms. Elaine Shin provided *some* of the requested material and noted in her covering letter that she was not providing all of the material.¹³² Although this package of material was substantially incomplete, it was clear that several witnesses, including Drs. Koren and O’Brodivich, had provided incorrect allegations and testimony. In her reply on March 30, Ms. Lacey wrote that Dr. Olivieri disputed these allegations and testimony, and that:

The credibility of Dr. Koren and Dr. O’Brodivich, and the credibility of Dr. Olivieri, are clearly at issue.... there is ample evidence that Dr. Koren has set out to destroy Dr. Olivieri’s reputation... he has already lied to... the Hospital’s investigator [Ms. Humphrey] into the hate mail affair...¹³³

Ms. Lacey again asked for all of the relevant material and for the opportunity for Dr. Olivieri to provide evidence from medical experts. She closed her letter with the request:

However, if we are not able to resolve these matters in a mutually agreeable way, we would ask that you consider whether the MAC would co-operate with Dr. Olivieri in bringing the disputes about process and disclosure before the courts for adjudication in an expeditious manner.¹³⁴

In early March 2000, the MAC had requested through counsel that Dr. Olivieri appear before it on April 12, 2000 and make any written submission by April 5.¹³⁵ Ms. Lacey informed this Committee of Inquiry that after she wrote requesting further and better disclosure on March 30, she had discussions with MAC counsel in early April who told her that the MAC would consider her request, and that counsel would reply as to whether the request would be granted, but that this would be a decision of the MAC.¹³⁶ Ms. Lacey said that she had the impression that she would be informed of the decision on her request for disclosure *before* any action was taken by the MAC. On April 24, 2000 Dr. Olivieri told this Committee of Inquiry that she understood that the date of her appearance before the MAC had been deferred until May 1, and that Ms. Lacey expected to receive additional documents beforehand.¹³⁷

(12) Referral to the CPSO & the University

After normal office hours on April 26, 2000 a letter arrived by fax from counsel Mr. Stockwood for the MAC to counsel Ms. Lacey for Dr. Olivieri advising that the MAC “met again yesterday and finalized its decision.”¹³⁸ It had done so *without* providing additional disclosure of documents or hearing a response from Dr. Olivieri. The faxed letter also said that the MAC’s report would be considered by the Board the next day, April 27. On April 27 the Board held a press conference and, with the MAC, publicly referred five allegations, cast in the form of “concerns,” to the College of Physicians and Surgeons of Ontario (CPSO) and the University of Toronto.¹³⁹ They thus

publicly caused serious damage to Dr. Olivieri's reputation in circumstances where she had no fair opportunity to respond. This action also imposed on her two more time-consuming, expensive processes of responding to CPSO and the University.

Dr. Becker, the MAC Chair, then wrote to the CPSO and the University on May 2, 2000 referring "concerns" involving "patient care" to the Complaints Committee of the CPSO, and "concerns" involving "research" to the University's Faculty of Medicine, under the Faculty's Framework for the Ethical Conduct of Research.¹⁴⁰ His letters made no specific allegations that any particular CPSO regulation, or University regulation, had been breached. Thus Dr. Olivieri was placed at a serious disadvantage in responding to either body, since she was not informed what regulations she was alleged to have breached.

Dr. Olivieri reported to us that she submitted a written brief to each body in the summer of 2000, in response to the referrals made by Dr. Becker.¹⁴¹ At the time this report was completed, neither the CPSO or the University had proceeded to a full inquiry.

It is relevant to consider events that likely would have followed a decision adverse to Dr. Olivieri's employment status, had the MAC brought recommendations for action against her to the Board and the Board approved them. She would then have been able to seek a remedy through administrative law procedures, and in view of the procedural unfairness of the MAC inquiry, such a case would have presented a reasonable prospect of success on judicial review. In an administrative law proceeding, greater disclosure might be required, giving an opportunity to examine the allegations and testimony by Drs. Koren and O'Brodovich and others in a rigorous fashion. As we have documented here, the allegations were without foundation, and the testimony was incorrect and misleading.

Some of Dr. Koren's MAC testimony was not only incorrect but dishonest, and he was closely associated with other adverse witnesses. In the disciplinary letter he received from the Hospital and University presidents on April 11, 2000, he was advised that he could be subject to further discipline if it were to be proved that allegations he made against Dr. Olivieri in the Naimark Review were based on evidence he fabricated. The presidents noted that he had "thrown away" a computer that might have provided proof. In the case of his MAC allegations, he gave supporting testimony that was contradicted by letters he himself had written or by other documents in his possession (see sections 5P(9 and 10) and section 5R).

(13) A different view

It is relevant to note the contrasting views of Dr. O’Brodivich, Pediatrician-in-Chief of the Hospital for Sick Children, and Dr. Baker, Physician-in-Chief of The Toronto Hospital (TTH), on Dr. Olivieri’s conduct during the post-trial, EDR period. Dr. O’Brodivich accused her of misconduct in matters of patient care, while Dr. Baker expressed full confidence in her.¹⁴² After thalassemia patients reach a certain age, their care is provided in the hospital across the street (TTH). In 1997 Dr. Olivieri was Director of the Hemoglobinopathy programs in both hospitals and the treatment protocols were similar.¹⁴³ Dr. Baker told us that even though Dr. Olivieri is a demanding and outspoken person, and not always easy to deal with, her excellence in research and patient care more than makes up for it, and he would be pleased to have many more people like Dr. Olivieri on his staff. In contrast, Dr. O’Brodivich cooperated with Dr. Koren in actions damaging to Dr. Olivieri, which could have led to the destruction of her career.

It was open to the MAC to invite Dr. Baker to provide information,¹⁴⁴ but it appears from the documents available to us that this was not done.

(14) Allegations by Apotex

Underlying the MAC allegations were purported issues of patient safety. The actual facts of the matter are that for transfusion-dependent thalassemia patients, whether on standard or experimental iron-chelation therapy, two critical safety measures are hepatic iron concentration (HIC) and hepatic histology. The data for HIC determination is normally obtained by liver biopsy (the alternative determination of HIC by SQUID is unavailable except at two centres outside Canada). HIC is the only accurate measure of effectiveness of iron-chelation, hence its importance as a safety measure. Where a risk of exacerbation of liver fibrosis has been identified, the only means assessing this in patients at risk is by microscopic examination of serial biopsy specimens. Liver biopsy is an invasive but low risk procedure that has been standard of care for such patients in both the Hospital for Sick Children and The Toronto Hospital for the past decade. In making allegations against Dr. Olivieri’s use of liver biopsy for the purposes she used it, Drs. Koren and O’Brodivich cast discredit the procedure itself and thereby placed themselves in opposition to the relevant medical literature, despite their lack of expertise in the relevant disciplines. (See section 5Q.)

Dr. Olivieri had identified both of the unexpected risks of L1 from biopsy data. Apotex disagreed with her findings, terminated the Toronto trials and attempted through legal warnings to prevent her from communicating these findings. Although the warnings impeded her, with legal support from CMPA she communicated the findings to regulatory agencies in 1996 and 1997, and published them scientifically. Apotex expressed strong objections to her

communications before and after the fact. (See sections 5E, 5F, 5H, 5I and 5K.)

Apotex made substantial efforts to counter Dr. Olivieri's adverse findings on its drug. Among these were communications with the Health Protection Branch (HPB) of Health Canada, in which the company used Dr. Koren's stated disagreement with her findings, and publications he co-authored with Apotex which supported the company's position (see section 5N(5)). The company also used his status as a co-investigator in the Toronto trials for which Dr. Olivieri was principal investigator. In a letter to HPB on August 13, 1996, the day before Dr. Olivieri was to meet with the regulatory agency, Dr. Spino wrote:

In a meeting on February 28, 1996, [Dr. Olivieri's] Co-Investigator, Dr. Koren, stated that he disagreed with her interpretation of the data.¹⁴⁵

A Priority Review Submission dated September 30, 1997 made by Apotex Research Inc. to HPB noted that "Dr. Olivieri has published several abstracts of her findings," and stated:

Dr. Olivieri's co-investigators and Apotex disagree with her interpretation and have published what we believe is the most appropriate analysis and interpretation of the data. ... All [Apotex sponsored] analyses suggest that there is no apparent change of effectiveness over time.¹⁴⁶

Therefore, the company considered Dr. Koren's status as co-investigator and his scientific credibility useful in putting forth to regulators its position on the efficacy (and hence) safety of L1.

In early 1998 Apotex made licencing submissions for L1 to regulators in several jurisdictions.¹⁴⁷ In these it downgraded the significance of the terminated Toronto trials and said that a one-year safety trial (LA-02) at international sites was the pivotal efficacy and safety trial. Discrediting Dr. Olivieri and her work was an aspect of these submissions. The company then made similar allegations to HSC. (See sections 5L, 5Q and 5U.) One of Apotex's allegations against Dr. Olivieri was made in a letter from Dr. Spino to Dr. O'Brodovich on May 22, 1998, namely, that her clinical monitoring of patients on L1 under EDR was unauthorized research.¹⁴⁸ It is clear from the context of the letter that the specific monitoring he referred to was HIC determination through liver biopsies. Later, Drs. Koren and O'Brodovich put forward similar allegations to the MAC (see sections 5P(10) and 5Q). As discussed earlier, the MAC believed these allegations and, together with the HSC Board, took public action against Dr. Olivieri on April 27, 2000. This action was taken two weeks after HSC and the University publicly announced that Dr. Koren had been disciplined for "gross misconduct," including persistent "lying,"¹⁴⁹ in relation to his anonymous letters.¹⁵⁰ This public

discrediting of Dr. Olivieri by HSC was later used by Apotex in legal proceedings to discredit Dr. Olivieri and defend the reputation of its drug.¹⁵¹

*(15) Conclusions**

1 | We find that Dr. Olivieri did answer the five MAC “questions” satisfactorily. Even though she was placed at a severely unfair disadvantage by having no knowledge of the allegations and testimony the MAC had received from its witnesses, Dr. Olivieri’s three-volume submission of October 1999 did in fact answer the questions the MAC stated to her. However, her response was extensive, and some of it necessarily technical, requiring diligence to fully understand it. It appears from the errors of fact and interpretation in the reports of the MAC and its subcommittee that they may have failed to exercise the level of diligence appropriate to the seriousness of their task. Had Dr. Olivieri been aware of the specific allegations, or anticipated the apparent lack of diligence of MAC members, she could have highlighted or summarized the relevant material (from the supporting documents she enclosed) in the covering brief to her MAC submission.

2 | The MAC proceedings were fundamentally flawed by unfairness. Allegations and testimony against Dr. Olivieri were received by the MAC and given credence, despite their being contradicted by the documentary record and the medical literature. None of the allegations and testimony were disclosed to Dr. Olivieri until after she had submitted her detailed response to the five “questions,” and after the MAC subcommittee had issued a report that was endorsed by the full MAC, despite written assurance from the Chair of the MAC subcommittee that such information would be disclosed.

3 | Most prominent among the witnesses adverse to Dr. Olivieri were Drs. Koren and O’Brodivich, who cooperated in putting forward testimony that was incorrect, incomplete, or misleading. Some other witnesses providing incorrect, incomplete, or misleading testimony had close associations to Dr. Koren.

4 | Dr. Moore provided mistaken, incorrect testimony that a research trial of L1 (namely, the long-term trial) continued after both trials had in fact been terminated. As REB Chair, she had available the termination notice for the long-term (LA-03) trial that was signed by Dr. Olivieri and her Division Chief Dr. Freedman in July 1996 and stamped as received by the REB on August 1, 1996.

A significant, unanswered question is: Why was this formal notice of termination of the long-term trial not provided to the Naimark Review and the MAC inquiry? Instead of this, Dr. Moore put forward what are in essence

*Our conclusions in this section rely also upon other sections, notably the section (5Q) on liver biopsy which is pertinent to MAC questions 5 and 1.

opinions, in her February 27, 1997 and June 3, 1998 letters to Dr. O’Brodivich (that were made available to the Naimark Review and the MAC inquiry), and in her testimony to the MAC—opinions that were incorrect and contradicted in primary documents.

5 | The allegations and testimony by Drs. Koren and O’Brodivich pertaining to liver biopsy were contradicted by medical literature, and also by established practice in the thalassemia clinic in their own hospital. The MAC called no witnesses who were experts in the relevant medical disciplines; instead it uncritically accepted as true, testimony from these persons without recognized expertise in this field.

6 | The allegations and testimony by Drs. Koren and O’Brodivich pertaining to liver biopsy, and purportedly unauthorized research, were similar to incorrect allegations and statements made earlier by Apotex.

7 | Dr. Koren behaved dishonestly: he was in possession of documents contradicting testimony he gave to the MAC, some of which he himself had written and signed; and he was not truthful about when and how he had been informed of the newly identified risk of progression of liver fibrosis. Dr. Koren was disciplined by the Hospital and the University on April 11, 2000 for his “gross misconduct,” including extensive “lying,” in connection with anonymous letters against Dr. Olivieri, sent during the period when he also provided incorrect testimony against Dr. Olivieri to the Naimark Review and to the MAC. These facts should have led the MAC and the Board to carefully examine his allegations and their possible influence on other MAC witnesses, prior to taking the very serious action it took against Dr. Olivieri on April 27, 2000. We have no evidence the MAC or the Board did this.

8 | Apotex used statements and publications by Dr. Koren, and his status as a co-investigator in the Toronto trials, in communications with regulators.

9 | The Hospital for Sick Children and the University of Toronto have a responsibility to review and address the conduct of Dr. Koren in the MAC proceedings.

10 | The MAC of the HSC terminated its proceedings before reaching specific conclusions. Instead, on April 27, 2000, the Board of Trustees and the MAC referred enumerated lists of allegations framed as “concerns” to the CPSO and the University in a highly public way, with consequent unjustified severe damage to Dr. Olivieri’s reputation.

11 | The Board of Trustees has a responsibility to ensure that, when the Hospital's Medical Advisory Committee investigates the conduct of a member of the Hospital's medical staff, a level of procedural fairness commensurate with the seriousness of the allegations is provided. Clearly the Board considered the allegations embodied in the five MAC "concerns" to be very serious, because it approved sending them to the CPSO and the University. At a minimum, the Board should have ensured that:

- there was full and timely disclosure to Dr. Olivieri of the allegations and testimony against her;
- Dr. Olivieri was provided with a full and fair opportunity to respond; and
- the Board itself had a full report on responses made to the MAC by Dr. Olivieri and her counsel, including the requests made for procedural fairness;

prior to taking the very serious action it took against her on April 27, 2000.

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5Q | The MAC Allegations in regard to Liver Biopsies

[L]iver biopsy is safe in children ... [the data] dispel the myth that this is a dangerous procedure in young patients. Based on the information from this large series, physicians should be encouraged to obtain, and rely upon, the results of liver biopsy in decisions regarding medical therapy....*

(1) Overview

IN THE MEDICAL ADVISORY COMMITTEE (MAC) proceedings, allegations were brought forward that Dr. Olivieri had used liver biopsies inappropriately. They alleged that this was a risky procedure and that the biopsies in question were done for research, not to guide patient care. Neither of these individuals is an expert in the treatment of thalassemia major, their allegations were not disclosed to Dr. Olivieri, and the MAC did not consult independent experts, yet the MAC believed the allegations. The allegations would easily have been refuted by checking the medical literature, where it is clear that liver biopsy is indicated, safe and widely used to guide the ongoing therapy of patients with thalassemia major, and quite specifically indicated in the circumstances in which they were used by Dr. Olivieri. Because the Hospital's Medical Advisory Committee apparently did not appreciate this, and the Board of Trustees relied upon the MAC in taking public action against Dr. Olivieri in April 2000, it is useful to discuss the allegations in some detail.

The MAC and its *ad hoc* subcommittee focussed on the series of biopsies done in the period February–April 1997, after the risk that L1 could cause progression of liver fibrosis was identified. The most extensive and detailed allegations, including that Dr. Olivieri did these “potentially life threatening” biopsies simply for research purposes, were made by Dr. Koren in his letter to the MAC in December 1998, and in his testimony in January 1999.¹ Allegations similar to some made by Dr. Koren were made by Dr. O’Broovich in his letter and testimony to the MAC in January 1999.²

An important question is: What were the origins of the allegations that liver biopsy is a risky procedure and that the biopsies in question were not done for clinical care but instead for research? In the extensive documentary record of the period after Apotex terminated the Toronto L1 trials, such allegations were first made a non-physician source, Apotex Vice-President for Scientific Affairs Michael Spino, Pharm.D., in March 1997. This was a month after Dr. Olivieri had identified that L1 posed a risk of progression of liver

*E. Angelucci *et al.*, “Needle liver biopsy in thalassemia: analyses of diagnostic accuracy and safety in 1184 consecutive cases,” *British Journal of Haematology*, 89 (1995), pp. 757–761 (quotation from p. 761).

fibrosis, and during the period when Apotex was attempting to suppress information on this risk through legal warnings to Dr. Olivieri. Apotex Research Inc. made similar statements against the use of liver biopsy in a document prepared for a regulatory submission in January 1998, in which it was also stated that the short-term LA-02 trial at international sites (whose protocol did not specify baseline liver histology and liver iron concentration for all participants) was the pivotal efficacy and safety trial for licencing purposes. In May 1998, Dr. Spino made allegations against Dr. Olivieri's use of liver biopsy to Dr. O'Brodovich. The allegations made during the MAC inquiry by Drs. Koren and O'Brodovich against Dr. Olivieri's use of liver biopsy were similar to statements made earlier by Dr. Spino and Apotex Research Inc.

In this section, we outline the allegations, relevant background information from the medical literature, specifications in the REB-approved protocols for the trials, and the information provided to patients on L1 —both those enrolled in the trials, and those treated with the drug under the subsequent non-trial EDR arrangement. In addition, we refer to regulatory information from the European Communities where Apotex was granted a licence in 1999 to market L1 in restricted circumstances. Upon reviewing the facts and circumstances of the allegations concerning liver biopsies, we have concluded that the allegations by Dr. Spino and Apotex Research, and the similar allegations subsequently made by Drs. Koren and O'Brodovich, are incorrect and unfounded.

(2) An important guide to therapy

Patients with thalassemia major are dependent on regular blood transfusions and consequently are subject to iron loading of organ tissues, unless they are receive effective iron-chelation treatment. Iron loading causes serious damage over time, including fibrosis of the heart and the liver. Transfusion dependence can also result in serious liver damage, including fibrosis, through infection by the hepatitis C virus. Liver fibrosis, if unchecked, can progress to cirrhosis. The situation was summarized by Drs. Olivieri and Brittenham in their 1997 review article:

The liver is a major repository of transfused iron. Hepatic parenchymal* iron accumulation, demonstrated after only 2 years of transfusion therapy, may rapidly result in portal fibrosis in a significant percentage of patients: one center has observed portal fibrosis in a high percentage of biopsies in children under the age of 3 years. In young adults with thalassemia major, in whom liver disease remains a common cause of death, viral infection and

*The parenchymal cells are the working cells of the liver.

alcohol ingestion may act synergistically with iron in accelerating the development of liver damage.³

In order to detect fibrosis, microscopic examination of a sample of liver tissue (histology) is required, and in order to determine whether it is progressing, serial extraction of samples over time is required. These are obtained by means of liver biopsy. Although this is an invasive procedure, with modern equipment it is now much safer and more precise than it used to be.⁴ Unless a new risk is identified or there is other clinical indication, intervals between biopsies are normally well-spaced—annually, for example.

The procedure of serial liver biopsy has been used to assess the adverse effects of iron loading in frequently transfused patients from the 1970s onwards.⁵ It has also been used for many years to assess the effectiveness of iron-chelation therapy, because the only accurate measure of tissue iron burden is hepatic iron concentration (HIC). (See section 2C.)

To date, the only proven treatment for iron-loading in thalassemia patients is iron-chelation therapy by the drug deferoxamine (DFO). After identification of the risk that L1 could cause progression of liver fibrosis, Dr. Olivieri transferred patients back to this therapy, so it is relevant to outline facts concerning DFO treatment. It was demonstrated in the mid-1970s that DFO, in addition to lowering body iron stores to a safe level, can arrest the progression of liver fibrosis caused by iron loading.⁶ Since then there have been several studies indicating that iron-induced liver and heart dysfunction is ameliorated by intensive deferoxamine therapy.⁷ Although it is licenced for therapy, there are toxicities associated with it that are of special concern in children. In the mid-1990s it was recognized that these toxic effects are associated with dosages that are too high in relation to body iron burden, owing to reliance on inaccurate measures of body iron burden (notably serum ferritin concentration), instead of HIC.

In 1995 an international expert panel on thalassemia major assembled by the National Institutes of Health (USA) reported:

Regular, accurate assessment of body iron loading is essential to guide chelation therapy and monitor its progress in the removal of iron. The assessment of liver iron using tissue from liver biopsy or noninvasive measurements of hepatic magnetic susceptibility using the SQUID (superconducting quantum interference device), which provides quantitatively equivalent results, remains the best methods for the determination of body iron loading.⁸ *

The 1995 NIH panel noted that serum ferritin concentration, though frequently used to estimate body iron burden, is an inaccurate measure, a

*Because only two laboratories, one in the USA and one in Germany, have the required SQUID equipment, this accurate alternative to liver biopsy for assessment of body iron burden is not widely available.

fact by then established in the literature. It nevertheless continued to be used in some centres as the primary guide to chelation therapy, but its inaccuracy was recognized in at least one of these centres in the late 1990s.⁹

Studies have shown that if the DFO dosage is precisely titrated in accordance with the patient's current HIC level, its toxicities can be significantly reduced. Dr. Olivieri's 1999 review article, with extensive references to the literature, reported that:

A balance between the effectiveness of deferoxamine and its toxicity—the latter observed primarily in the presence of relatively low iron burdens—can be maintained through regular determinations of body iron burden.... Determination of hepatic iron concentrations in liver-biopsy specimens obtained with ultrasonic guidance is safe and permits rational adjustments in iron-chelating therapy.¹⁰

Because of such advances in the understanding and treatment of transfusion-dependent patients, liver biopsy has been a component of “standard of care” in the hemoglobinopathy clinics in HSC and The Toronto Hospital (TTH) for a number of years, independently of whether or not the patients are in a research trial.

Dr. Olivieri reported to this Committee of Inquiry that it is a matter of documented record that in the Hemoglobinopathy Clinic of the Hospital for Sick Children during the past decade, liver biopsies have been used for diagnostic purposes for a substantial number of patients each year, independently of whether or not the patients are on standard therapy or on an unproven treatment under EDR, and independently of whether or not they are in a research trial.¹¹ During the same period the procedure was also standard in TTH where adult patients receive their care, as the liver pathologist Dr. Ross Cameron confirmed:

I have worked with Dr. Nancy Olivieri at TTH since 1990. Liver biopsies are part of standard of care for patients with liver disease. As thalassemia and sickle cell patients are at risk of liver disease, since 1990 their standard of care at TTH has included liver biopsies on an annual or biannual basis.¹²

Dr. Olivieri reported to us that, because of these facts, the allegations against her use of liver biopsies had come as a considerable surprise when they were disclosed to her in March 2000.

(3) The allegations by Drs. Spino, Koren, and O’Broovich

These allegations, that liver biopsy was risky and that Dr. Olivieri's use of it was for research not for management of the clinical care of patients, can be followed chronologically through the documentation.

(i) There was an exchange of correspondence in early March 1997, in which Apotex Vice-President Dr. Spino tried to persuade Dr. Brittenham not to

present an abstract on the risk of progression of liver fibrosis at a conference in Brugge scheduled for March 14–15 (Dr. Olivieri had already withdrawn as co-author because of Apotex’s legal warnings, on CMPA legal advice—see section 5I).¹³ Dr. Brittenham replied that he would proceed because

hundreds of patients in Europe continue to be treated with deferiprone because of lack of knowledge of this unforeseen complication of therapy.¹⁴

Dr. Spino responded the following day, March 7, 1997, suggesting that presenting findings on the risk of progression of liver fibrosis would be viewed as a “precipitous” action, and requesting the Dr. Brittenham not make any presentation on the topic until after Apotex had made its own assessment of the data. In this letter, Dr. Spino made a general statement against the use of liver biopsy:

It has come to our attention that many physicians treating patients with thalassemia are already beginning to perform hepatic biopsies in these patients to determine if fibrosis is present. We are concerned that these patients may have undergone a needless, invasive procedure with its attendant risks and costs.¹⁵

(ii) March 6, 1997 was the day on which Dr. Olivieri held a group meeting with patients and parents to advise them that L1 should no longer be used and explain her reasons (notably the two unexpected risks she had identified: loss of sustained efficacy and progression of liver fibrosis). On the same day, Dr. Spino sent a letter to the senior hematologists in The Toronto Hospital and the Hospital for Sick Children, Dr. Baker and Dr. Freedman, promoting wider use of L1 in the two hospitals. Dr. Spino copied his letter to Dr. O’Brodivich. He appended a proposed schedule for monitoring patients on this unproven drug that was designed by Apotex staff and omitted annual liver biopsy (in this, it was similar to the LA-02 protocol—see below). Dr. Baker and Dr. Olivieri did not accept this proposal, but we have no record of any response from Dr. Freedman or Dr. O’Brodivich. (See section 5K(9).)

(iii) In August 1997, Dr. Olivieri sent to Apotex a draft copy of the abstract she intended to submit for the December 1997 ASH meeting. The abstract was based on HIC data from the charts of some patients who had been enrolled in the randomized trial LA-01, and concluded that L1 was significantly less effective than the standard drug DFO, to the extent that it posed a safety risk if used long-term. In a reply on August 27, 1997, Apotex strongly objected to this publication.¹⁶ (See below, and also section 5U(4).) A month later, Apotex made a “Priority Review Submission” to the Health Protection Branch (HPB) of Health Canada for licencing of L1 under the name Deferrum, in which it criticized Dr. Olivieri and disputed the validity of her adverse findings. In support of its contention, that adverse findings on

L1 published by Dr. Olivieri in several abstracts in 1996 and 1997 were inappropriate, the company said in this regulatory submission that:

Dr. Olivieri’s co-investigators *and* Apotex disagree with her interpretation and have published what we believe is the most appropriate analysis and interpretation of the data.¹⁷ (emphasis added)

Prominent among Dr. Olivieri’s co-investigators who published with Apotex was Dr. Koren, who had agreed to be listed as senior author on two abstracts published by the company in April 1997 (see section 5N(5)).

(iv) In early 1998, Apotex made licencing submissions for L1 to regulatory agencies in several jurisdictions. In these it claimed that the short-term safety trial (LA-02) at international sites was the “pivotal” efficacy and safety trial for licencing. Apotex said that the two Toronto trials—the randomized trial for comparison of L1 with standard therapy (LA-01) and the long-term efficacy and safety trial (LA-03)—were “supportive” studies to LA-02.¹⁸ The two unexpected risks of L1 identified in data of the LA-03 trial depended on the baseline and annual HIC and histology data that were provided for in the LA-03 protocol. The LA-01 protocol also included baseline HIC and histology assessments. However, the protocol for the LA-02 trial, designed as a one-year safety trial, did not include baseline assessments of liver histology or hepatic iron concentration (HIC). (See sections 5A, 5B and 5U.)

A document prepared by Apotex Research in January 1998 in connection with a regulatory submission said:

[B]ecause of its invasiveness, the assessment of body iron in liver biopsy samples is not generally accepted for the sequential determination of iron load in the clinical setting, although it does have limited application in clinical trials.¹⁹

This 1998 statement by Apotex was contradicted by the current medical literature, particularly that dating from 1995 onward, as the citations earlier in this section 5Q show. Nevertheless, the Apotex view was repeated by Dr. Spino later in 1998.

(v) Dr. Spino wrote to Dr. O’Broovich on May 22, 1998 about data Dr. Olivieri presented at the December 1997 ASH meeting, the abstract for which was published in the journal, *Blood*.²⁰ Some of the reported data had been collected in 1996 and 1997 from the monitoring of patients who had been on L1 under Emergency Drug Release (EDR). Dr. Spino alleged that this constituted unauthorized research. The data Dr. Olivieri reported was on hepatic iron concentrations (HIC—some obtained by biopsy, some by SQUID) of some patients who had been in the randomized comparison trial (LA-01) cohort prior to its termination in May 1996, some of whom had continued on L1 after the trial. The abstract reported comparatively on some patients who had been on L1, and others who had been on DFO (deferoxamine—the standard

therapy).²¹ The abstract stated that the LA-01 trial had been terminated by the sponsor, Apotex, but that data from trial and post-trial monitoring was available on some patients in their charts. This chart-review abstract presented a strongly adverse finding on the efficacy and safety of L1 in comparison to DFO, as noted above.

In this letter to Dr. O’Brodivich, Dr. Spino wrote:

As you are aware, Apotex terminated the trials of deferiprone (LA-01 and LA-03) at the Hospital for Sick Children in May 1996.... Dr. Olivieri presented... results... in December 1997.... Would you please confirm whether or not patients... received notification that they were in a new trial, which was no longer being sponsored by Apotex, and whether or not this new trial received Ethics Committee [REB] approval at the Hospital for Sick Children.... we do not know if Dr. Olivieri received authorization from the Ethics Committee to start a new trial with our drug after Apotex had terminated the trial in that hospital [HSC].²² *

In summary, Dr. Spino’s allegation was that because some patients who had continued on L1 under EDR and were monitored for iron overload by the only accurate measure (HIC), and Dr. Olivieri published the results, she was conducting an unauthorized research trial. However, Dr. Olivieri was ethically and legally required to monitor the patients, in order to manage their treatment appropriately, and to be able to report the results of treatment as required under the EDR regulations. Furthermore, she had documented to the Hospital that patients would only be treated with L1 if they were fully informed of risks and agreed to be monitored. (See sections 5G and 5H.) The monitoring procedures were standard and clinically necessary, so did not constitute unauthorized research. It is important to note as well that at this time publication of chart review data did not require REB approval, and did not constitute unauthorized research.²³

(vi) Later, in a November 24, 1998 letter to Dr. Naimark, Dr. Spino referred specifically to the biopsies done on patients in early 1997. In this letter he alleged that Dr. Olivieri had continued to administer L1 “in order to collect more hepatic biopsy data,” thus again implying that she had been doing unauthorized research.²⁴

(vii) The Naimark Report did not address these liver biopsies as being an issue, and Dr. Naimark did not deposit Dr. Spino’s letter in the HSC library

*Dr. Moore was asked by Dr. O’Brodivich to comment on Dr. Spino’s letter. Her response on June 3, 1998 was that, contrary to Dr. Spino’s contention, there was no new trial, but rather, one of the terminated trials had “continued with full REB approval,” but without Apotex sponsorship. Dr. Moore and Dr. Spino both were wrong: there was no L1 trial in 1997, new or continued. Dr. Olivieri was copied of this letter by Dr. Moore and she then wrote to Dr. O’Brodivich on June 8, 1998, noting that both L1 trials had been terminated in May 1996. (See section 5K.)

archive. Dr. Spino's allegation appears not to have been pursued until Dr. Koren made similar allegations in his letter to the MAC, at the outset of its investigation in December 1998.²⁵ Among the various allegations in his letter, Dr. Koren put forward a hybrid of mutually contradictory contentions of Dr. Spino and Dr. Aideen Moore on whether there was any clinical trial of L1 in Toronto after May 1996. While Dr. Spino said (correctly) that Apotex had terminated both trials, and alleged (incorrectly) that the liver biopsies constituted unauthorized research, Dr. Moore said (incorrectly) that LA-03 had continued and was under REB jurisdiction, and she suggested that L1 patients from the LA-01 cohort had somehow been merged with the LA-03 cohort. It is well documented that Dr. Koren knew that both trials had been terminated: he had written and signed letters in 1996, 1997 and 1998 confirming this for both the LA-01 and LA-03 trials (cited in section 5P(9)). In his letter to the MAC, Dr. Koren did not directly state the opposite of what he had written in these earlier letters, but instead quoted from Dr. Moore's letter to Dr. O'Brodovich in which she said (incorrectly) that a trial had continued under REB approval.²⁶

Dr. Koren's direct allegation on liver biopsies was similar to that of Dr. Spino: that the liver biopsies done on fifteen patients during February—April 1997 were not clinically indicated, and that therefore they were done for research. He wrote to the MAC:

[S]he [Dr. Olivieri] did not seek approval to perform liver biopsies. ... I believe this is a research question that would necessitate a protocol and ethics approval. She never approached REB for this.

If this was not a research project, as Dr. Olivieri claims now, how could she perform liver biopsies on asymptomatic patients? None of the 15 patients brought by her in February '97 for liver biopsy had either serious liver enzyme elevations, high bilirubin, or clinical disease reflecting liver pathology. The clinical indications for liver biopsy are known and stringent. This is a potentially life threatening procedure. I believe it could not have been done on patients just because they had received L1, unless there was a research question.²⁷

The summary of Dr. Koren's testimony to the MAC on January 19, 1999 contains similar allegations:

Dr. Koren... stated that there were no cases of deteriorating liver condition in patients, yet biopsies were done. He further stated that in a normal situation, one would have consulted with Pathology. He said that if the study was being done for research purposes, it should have gone to the REB for approval for biopsy, prior to getting patients to consent.... Dr. Koren suggested that instead of immediate biopsies, Dr. Olivieri should have asked for hepatology consults first, to handle clinical management appropriately.²⁸

We discuss Dr. Koren's allegations in the next subsection.

(vii) Dr. O’Brodivich put forward an allegation similar to Dr. Koren’s in his letter to the MAC dated January 4, 1999, by raising a question and proposing an answer to it. Referring to the liver biopsies done on the same fifteen patients referred to above, Dr. O’Brodivich wrote:

The question is whether any or all of these patients had clinical evidence of liver disease (eg. abnormal liver function tests) and the biopsies were indicated from a medical point of view.²⁹

In other words, his question was whether the biopsies constituted unauthorized research. Dr. O’Brodivich did not explain in his letter to the MAC why he had not raised this question two years earlier, when Dr. Olivieri had repeatedly informed him that the biopsies were then being scheduled (see section 5K). Instead he proposed an answer to the question of whether the liver biopsies represented research by means of a one-sentence quotation from a 1998 article on a study of thalassemia patients on L1 in Switzerland:

Liver biopsy had not primarily been performed in any of the patients.³⁰

From the full text of Dr. O’Brodivich’s letter, the inference is that this sentence provided evidence that liver biopsy was not established as a guide to therapy for patients with thalassemia major, so that it must be a research procedure. By doing so, Dr. O’Brodivich misrepresented the substance of the article, as we discuss in the next subsection.

(4) Incorrectness of the allegations

As outlined earlier, there were two related clinical reasons why some patients on L1 were counselled to have biopsies in early 1997, if they had not recently had one. At the beginning of February 1997, Drs. Cameron, Olivieri and Brittenham had determined that L1 was the probable cause of progression of liver fibrosis observed in some patients in another group. The only way in which it could be ascertained whether any other patients had experienced this adverse effect while on L1 was by liver biopsy. The other reason was to determine their future course of therapy, for which recent information on hepatic iron concentration (HIC) levels and fibrosis status were required. Dr. Olivieri decided that they should be returned to standard (DFO) therapy and the biopsy results were needed to determine the dosage, as well as the timing of DFO administration. In short, these liver biopsies were clinically indicated as necessary to ascertain each patient’s condition and to guide their individual therapy.

The fact that Dr. Olivieri subsequently included these results in her 1997 ASH abstract is not evidence that the biopsies represented unauthorized research. Contrary to the allegations, publication of data obtained from review of patients charts did not at the time require REB approval, as Dr.

Koren certainly knew, having published this in his textbook on clinical ethics (see section 5P(9)).

Although the allegations regarding these liver biopsies were without foundation, specific details put forward to the MAC by Drs. Koren and O’Brodivich are of interest, because these details should have led the MAC to subject their testimony to close scrutiny.

The Swiss Study. In his letter to the MAC, Dr. O’Brodivich relied on the 1998 article by the Swiss team of investigators, but confined himself to quoting a single sentence: “Liver biopsy had not primarily been performed in any of the patients.” He quoted that one sentence accurately, but the import of the article is clearly not what he suggested. To the contrary, the article demonstrates why liver biopsy is *necessary* as a guide to therapy in patients with thalassemia major, and contradicts his allegation that the biopsies done by Dr. Olivieri during February-April 1997 were not clinically indicated.

At a meeting in Malta in April 1997, Dr. Olivieri had reported the finding that L1 was the probable cause of progression of fibrosis in some of her long-term treatment group of patients. The Swiss investigators then undertook to assess this in their eleven patients who had been on L1 for several years. Their article states:

the Swiss group of β -thalassaemic patients with the longest known duration of L1 therapy was *asked to submit to a liver biopsy* in May 1997, in order to study their hepatic histopathology and iron concentration.... Re-evaluation (of hepatic iron concentration) by SQUID planned for 1997 was cancelled in favour of the determination of liver iron in biopsy specimens ... because the assessment of *hepatic histology had to be given full priority*.³¹ (emphasis added)

In other words, because a *risk* of progression of liver fibrosis had been identified in data from one long-term study, the LA-03 trial in Toronto, the Swiss investigators considered that assessment of their patients for this adverse effect was indicated. They made the assessment by the only means of doing so—biopsy. They found varying degrees of fibrosis in a majority of their eleven patients, with the most serious cases in those who were hepatitis C positive.³² However, these investigators were *not* able to determine whether their patients had experienced *progression* of fibrosis, because of what they themselves called:

the serious flaw of lacking baseline assessments of hepatic histology and iron concentration [HIC].³³

The actual import of the one sentence Dr. O’Brodivich quoted was that the patients in the Swiss study had not undergone a baseline liver biopsy, and hence the study was flawed. The only way to remedy lack of baseline

assessments of hepatic histology is to start a new study, in which biopsies are done at the outset, or to re-start it from the time of the initial biopsy.

The Swiss investigators also reported that Dr. Olivieri's findings on the loss of sustained efficacy of deferiprone were confirmed in three of their nine patients on whom comparative HIC data was available (from a 1994 SQUID determination and from the 1997 biopsy determination). They added that for their group of patients in Berne:

Further studies may elucidate this apparent loss of efficacy as well as the striking diversity of long-term response to deferiprone, and *a repeat biopsy is planned* for 1999.³⁴ (emphasis added)

In view of what the authors actually reported, it is hard to understand how Dr. O'Brodovich could have construed the article by the Swiss team as implying that there was no clinical basis for the biopsies Dr. Olivieri arranged during February-April 1997. It was open to the members of the MAC to read the full article, rather than the one sentence put forward by Dr. O'Brodovich, but we have seen no evidence that they did so.

"A potentially life threatening procedure." This allegation by Dr. Koren is disposed of by reference to the study of 1184 liver biopsies, quoted at the beginning of this section 5Q. It was published in 1995, several years prior to Dr. Koren's allegation. Although possibly Dr. Koren had not read this particular article, this was not an isolated finding and corresponded to the experience with biopsies for thalassemia patients in Dr. Koren's own hospital, HSC. Indeed he was one of only two investigators for the long-term trial (originally termed the pilot study, and later termed the LA-03 study), and as a trial investigator he was responsible for the documents required for ethics approval. Consequently, he ought to have read and agreed with the "Patient Information Form" for that trial. That form explained liver biopsy to trial subjects in the following terms:

Liver biopsy involves the freezing of the skin over the liver (located in the right lower abdomen) and insertion of needle to obtain a small piece of liver tissue, which would then be stained and weighed for iron content. This procedure carries a small risk of bruising or bleeding from the puncture site, and the discomfort of local freezing itself, but of all liver biopsies performed by the experts at The Hospital for Sick Children during the last 10 years, only a very small percentage of biopsies has resulted in this type of complication. No complication has resulted in death, or even extra days of hospitalization. Liver biopsy will be performed at the onset of study and after 12 months of therapy.³⁵

It is also of note that the 1184 biopsies reported on by Dr. Angelucci *et al.* were performed "without ultrasound guidance."³⁶ The authors wrote that,

“Both the safety and diagnostic accuracy... can presumably be increased with the use of ultrasound guidance.”³⁷ Ultrasound guidance is used for biopsies of patients treated in the clinics at the Hospital for Sick Children and The Toronto Hospital, “with large numbers of patients regularly undergoing liver biopsies under ultrasound guidance” safely.³⁸

Therefore it is likely that Dr. Koren knew that his characterization of liver biopsy as “Potentially life threatening” was a significant exaggeration. It was open to MAC members to review HSC records in this regard, as well as the relevant documentation provided by Dr. Olivieri in her October 1999 submission, but we have seen no evidence that they did so.

Dr. Koren’s testimony as to when liver biopsies are clinically indicated. Dr. Koren alleged to the MAC that the biopsies done on patients by Dr. Olivieri during February—April 1997 were not clinically indicated because there were no characteristic signs of liver abnormality. His testimony was to the effect that progression of liver fibrosis can be detected by standard liver function tests (i.e., by tests other than histological examination of biopsy slides). This is not correct. It is likely that he knew it was incorrect, because by his own account he had received copies of Dr. Olivieri’s February 1997 report of the risk of progression of liver fibrosis both from her and from Apotex.³⁹ This report stated:

In our patients with progression of hepatic fibrosis during therapy with deferiprone, no characteristic abnormalities in liver function tests were observed.⁴⁰

Dr. Olivieri included a copy of this report in her submission to the MAC in October 1999, but we have seen no evidence that the MAC carefully examined and understood this report.

(5) Safety precautions for the use of L1

The orally active iron-chelator L1 had been shown to have toxic effects in animal models, and to have acute toxicity effects in several humans in preliminary trials outside Canada. These were among the reasons why Ciba-Geigy, a manufacturer that held commercial rights to L1 before Apotex acquired them, decided not to develop it as an alternative to DFO.⁴¹ (Ciba-Geigy—now Novartis—markets DFO, under the trade-name “Desferal.”) However, L1 had also shown some promise in trials involving small numbers of patients in London, and this encouraged the hope that a patient population in which it was sufficiently safe and effective could be identified. Because its efficacy and safety were unproven, regular testing of the liver and other organs in patients taking it were a part of Dr. Olivieri’s L1 trials from the outset.⁴² Quite aside from whatever toxicities L1 might have by itself, if it proved not to be effective this would allow the known harmful consequences of iron-loading

to worsen in patients on the drug. Since the accurate measure of tissue iron stores is hepatic iron concentration (HIC—determined from liver biopsy samples), in addition to being the primary measure of efficacy in the trials, it was a principal determinant of safety.

During the period since 1989, there have been three different administrative circumstances in which patients have been treated with L1. These are:

(i) in a clinical research trial, with the protocol approved and the trial monitored by a research ethics board (REB). This was the situation in Toronto from 1989 until May 1996 when Apotex terminated both trials there;

(ii) under an emergency drug release (EDR) program of a government regulatory agency. This is a therapeutic situation, as distinct from a research trial, in which the treating physician is responsible to government regulators, rather than a hospital REB. This was the situation in Toronto, after Apotex agreed to begin re-supply of the drug under EDR in June 1996 and until early 1997, when Dr. Olivieri decided to discontinue L1 treatment and return patients to standard therapy;

(iii) therapeutic use in the European communities following the granting to Apotex of restricted license to market L1 in 1999.*

We review the safety precautions in each of these circumstances.

I. THE PERIOD OF THE TRIALS (1989–1996)

The REB-approved protocols for both the non-randomized pilot study (1989–93) and its continuation termed LA-03 (1993–96), and the randomized, comparison trial LA-01 (1993–96), contain various safety precautions involving regular testing of organ systems. Initially, hepatic iron concentrations (HIC) were obtained only from chemical analysis of biopsy samples, but later Dr. Olivieri began a research collaboration with Dr. Brittenham, so HIC determinations by SQUID then became available. This required patients to travel to Dr. Brittenham's laboratory in Cleveland (their airfare was covered by Apotex funds from 1993 until the termination of the trials). However, serial biopsies continued to be used for histology, and for HIC in the cases of patients unable to travel to Cleveland.

The importance of liver biopsy as a guide to treatment for patients with thalassemia major was made known to officials of HSC from the outset of both trials. The procedure was discussed in the protocols Dr. Olivieri submitted to the REB, and in the applications she and Dr. Koren made to MRC

*L1 has been licenced in India, which has a relatively weak regulatory infrastructure, since 1995.

for funding for the pilot study. It was discussed also in the application under MRC's joint university-industry program for the randomized study (LA-01). For instance, a 1990 protocol for the pilot study (later termed LA-03) approved by the REB said:

We have demonstrated that iron excretion induced by the administration of... [L1] is comparable to that induced by... DFO in short term studies. We are now beginning long-term studies.... Evaluation of the efficacy of this agent as an alternative to DFO will depend on careful documentation of reduction in body iron. Since liver iron concentrations [HICs] have been documented during the initial studies of DFO, this is the endpoint to which L1's efficacy should and must be compared. ...serum ferritin is... at best an indirect assessment of body iron overload.... Serum Ferritin is affected by other variables... [and] is not an informative serial measurement....⁴³

Like the protocol for the pilot study, the REB-approved protocol for the randomized, comparison trial (LA-01) specified baseline liver biopsy for all patients on enrolment. It discussed the equivalence of HIC measurements by biopsy and by magnetic susceptometry (SQUID), and continued:

liver biopsies, but not SQUID, allow assessment of the histopathology of the liver.... the histology... is important to the proper clinical management of the patients.⁴⁴

Patients could opt to refuse liver biopsy after enrolment in the trial, if they could travel to Cleveland for SQUIDs, but they were counselled to have annual biopsies for histology purposes. The LA-03 protocol (a revision of the protocol for the original pilot study) had similar provisions.⁴⁵

II. THE EDR PERIOD (1996–1997)

From June 1996, those trial subjects for whom L1 was still seen to be beneficial, and who after being fully informed of the risks wished to continue on the drug, were allowed to continue under the EDR arrangement of Health Canada. Dr. Olivieri continued to be their treating physician. L1 was unproven as to efficacy and safety, and therefore a potentially dangerous drug. Under international ethical guidelines for physicians, and under the EDR provisions of the Canadian *Food and Drugs Act* and *Regulations*, Dr. Olivieri had obligations to safeguard her patients and to inform them and the relevant authorities of the results of treatment. In particular, she had a legal obligation as “the practitioner” to:

report to the manufacturer of the new drug and to the Director on the results of the use of the new drug in the medical emergency, including information respecting any adverse drug reactions encountered.⁴⁶

However, since there was no longer a research trial, under HSC policy and practice Dr. Olivieri was not required to inform the REB. The patients had a life threatening genetic disease, the primary treatment for which,

regular transfusion, was also life threatening unless their tissue iron burdens were kept at a safe level by this chelation therapy. Patients on the standard chelation therapy have to be regularly monitored, and the chelator L1 was unproven, so the effects of using it had to be monitored with no less rigour than those on standard therapy, in order to safeguard them. As discussed in section 5H(1), Dr. Olivieri set out in writing the conditions under which she would agree to serve as the practitioner for administration of L1 to patients under the EDR program, including the monitoring tests to be used. “Annual liver biopsy” was expressly listed as one of the tests and Dr. Koren co-signed the letter, which stated that these tests “provide the minimum amount of monitoring necessary to ensure patient safety on this experimental chelator.”⁴⁷*The continuing patients agreed to these conditions.

After she identified the risk of progression of liver fibrosis in early February 1997, Dr. Olivieri met with patients to inform them of this new risk. She counselled those who had not recently had annual liver biopsies to have one in the near future and explained the reasons why they were clinically indicated (see section 5K and this section 5Q). The subcommittee of the MAC charged with investigating Dr. Olivieri’s conduct reviewed “the charts of the patients in question,” and confirmed that: “[i]n every instance a consent was secured [from the patient] for liver biopsy,” and “[a]ll patients underwent the procedure without complication.”⁴⁸

III. RESTRICTED THERAPEUTIC USE OF L1 IN EUROPE

Another administrative framework for the use of L1 began in August 1999, when Apotex was granted a European marketing authority for the drug. This was restricted to patients unable to comply with the standard treatment, deferoxamine. While this applied only in the European Communities (EC), the conditions set out in the licencing approval report are relevant to our discussion. The “European Public Assessment Report” (EPAR) issued by the EC on August 12, 1999 contains the following passages.

*As in several other significant instances, Dr. Koren contradicted himself in written statements, in this case regarding monitoring of patients on L1 under EDR. He co-signed with Dr. Olivieri the letter to Dr. Zlotkin on July 15, 1996, stating that monitoring would be done and specifying that the assessments would be the same as in the terminated studies, including annual liver biopsy. However, on May 14, 1998, he wrote to Dr. Buchwald that he was “not aware that Dr. Olivieri continued to monitor study endpoints, and especially liver iron.” In fact, assessment of liver iron (HIC) was a primary reason why the July 15, 1996 letter specified “annual liver biopsy,” as Dr. Koren must have known, having been an investigator in the L1 trials throughout their duration, 1989–1996.

The approved indication [the restriction] is for the treatment of iron overload in patients with thalassemia major for whom deferoxamine therapy is contraindicated or who present serious toxicity with deferoxamine therapy.

...

The CPMP [Committee for Proprietary Medicinal Products] recommended that the Marketing Authorisation should be granted “under exceptional circumstances” because of the fact that in the present state of scientific knowledge, comprehensive information on safety and efficacy of the medicinal product cannot be provided.⁴⁹

The EPAR “Package Leaflet” to be provided to physicians and patients contains “special warnings,” including:

Your doctor will also ask you to come in for tests to monitor body iron load. In addition he or she also might ask you to undergo liver biopsies.

The “Scientific Discussion” section of the EPAR refers to the 1998 article by Dr. Olivieri *et al.* presenting the findings that L1 itself may cause progression of liver fibrosis.⁵⁰ It goes on to say:

In thalassemia patients there is an association between liver fibrosis and hepatitis C. Special care must be taken to ensure that iron chelation in patients with hepatitis C is optimal. In these patients careful monitoring of liver histology is recommended.

In summary, in the restricted *therapeutic* use of L1 which they have authorized, the European regulators specify precautions which are consistent with those used by Dr. Olivieri during the EDR period in Toronto.

(6) Medical Specialization

Because of advances in medical science and the application of new diagnostic procedures and treatments by highly trained clinical specialists, many children born with formerly fatal diseases can now survive into adulthood with reasonably good quality of life. The Hospital for Sick Children is a world leader in the clinical care of children with such diseases. It has many clinical research physicians on staff who are internationally recognized for their contributions both to science and to specialized clinical management of diseases. An important way in which new diagnostic methods and treatments come into wide use by specialists, is through the publication of review articles in leading medical journals.

Dr. Olivieri is one of the HSC staff who has advanced the understanding and treatment of diseases in her fields of medicine. This is demonstrated by publication of a review article by her on “The β -Thalassemias” in *The New England Journal of Medicine*,⁵¹ and a review article with Dr. Brittenham on “Iron-Chelating Therapy and Thalassemia” in *Blood*.⁵² These are two leading journals internationally. Dr. Olivieri’s work and her clinical and research programs are highly regarded by leaders in the field,⁵³ and her standing has been acknowledged by Dean Aberman: “I consider Nancy Olivieri an outstanding clinical investigator and an authority of international stature on hemoglobinopathies.”⁵⁴

Therefore, it is hard to understand why the HSC Medical Advisory Committee and Board of Trustees believed the allegations concerning her management of patient care—allegations made by persons who are not experts in the relevant fields, and that were contradicted by available documents. The Board and the MAC took serious actions against her based on their belief, without consulting any experts to verify the accuracy of the allegations, and apparently without carefully examining available documents. (See section 5P.)

(8) Conclusions

1 | The allegations concerning Dr. Olivieri’s use of liver biopsies made by Apotex staff, and by Drs. Koren and O’Brodivich, are incorrect and without foundation. The allegations by Drs. Koren and O’Brodivich were similar to, and subsequent to, those made by Apotex staff.

2 | Attempts to discredit Dr. Olivieri had the effect of serving the interests of Apotex, an aspect of whose licencing submissions for L1 was to attempt to discredit her, and to dispute the risks of the drug she identified.

3 | During the non-trial EDR period, Dr. Olivieri monitored patients because she was ethically and legally obligated to do so, and she monitored them in accordance with medical practice established in the literature, and standard of care in the HSC and TTH clinics.

4 | After Dr. Olivieri identified a risk of progression of liver fibrosis in data of one group of patients on L1 under EDR, she took appropriate, clinically indicated measures to assess whether patients in another group had experienced this adverse effect, and to guide their future course of therapy.

5 | When, in December 1998 and January 1999, Dr. Koren made his allegations concerning liver biopsies, he had already begun sending out his series of anonymous letters in an effort to discredit Dr. Olivieri. His allegations regarding liver biopsies were the most extensive and detailed the MAC received on this topic. They were incorrect, but were believed by the MAC and hence damaging to Dr. Olivieri. In fact, liver biopsy is established as a necessary guide to therapy for patients with thalassemia major, and one that is safe. It is also the only means whereby progression of fibrosis can be assessed. When Dr. Koren made his allegations, he was in possession of documents that contradicted his allegations, so he likely knew they were untrue. When, on April 27, 2000, the Hospital publicly referred allegations that originated in substantial measure with Dr. Koren to outside bodies, the Hospital and the University had already disciplined him for “gross misconduct,” including “lying” and “breach of trust.” In view of the documentary record, it is hard to believe that Dr. Koren did not bring forward his allegations to the MAC with intention to cause harm to Dr. Olivieri’s career and reputation.

6 | Dr. O’Brodivich was neglectful in putting forward serious allegations apparently without making serious effort to check their validity.

7 | The MAC and the HSC Board of Trustees did not live up to their responsibility to ensure the level of due process and diligence required in such a serious matter. (See section 5P.)

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5R | The Central Role of Dr. Koren in the L1 Controversy

IT IS CLEAR FROM THE extensive documentation available to this inquiry that Dr. Koren has played a central role throughout in the L1 controversy. Independently, HSC's harassment investigator Ms. Humphrey reached this conclusion from her investigation:

Dr. Koren was the most constant individual at the centre or the heart of the L1 trials controversies and most of the issues and conflicts that appeared to have erupted in the wake of the discontinuance of the L1 trials in May of 1996.... All these issues appeared to have involved Dr. Koren in a very direct and personal sense.... [T]here was no other individual... who appeared to have anywhere near the level of detailed knowledge of and direct involvement in the range of post L1 controversies as Dr. Koren.¹

(1) Dr. Koren's involvements in the Naimark and MAC inquiries

The HSC Board of Trustees took action against Dr. Olivieri on receiving the Naimark Report in December 1998, and again on receiving the report of the Medical Advisory Committee (MAC) in April 2000. In each instance, adverse conclusions on Dr. Olivieri's conduct in the report provided the basis of the Board's action. These conclusions were based on incorrect information provided by several witnesses, notably Dr. Koren, Dr. O'Brodovich and Dr. Moore. In this subsection we briefly review their involvements, noting the prominence of Dr. Koren (see sections 5K, 5O, 5P and 5Q for details and citations).

Dr. Koren was one of the "primary submitters"² of information to the Naimark Review, and he submitted information through Dr. O'Brodovich, as well as directly. In the MAC inquiry he surpassed Dr. O'Brodovich in the extent and detail of his allegations on several matters. Dr. Koren's testimony may be distinguished from that of Dr. O'Brodovich or Dr. Moore (see below), in that it is documented that he put forward allegations and testimony that he knew to be incorrect. A central instance pertains to the terminations of the two L1 trials. Dr. Koren knew that both had been terminated and neither of them continued or reinstated, and recorded this fact in several letters he wrote between May 1996 and May 1998. He was in a position to advise Dr. O'Brodovich, the Naimark Review, and the MAC that Dr. Moore was mistaken in her contrary statements. It appears that he did not do so. Instead, he himself cited Dr. Moore's incorrect information to bolster his own testimony to the MAC, although he knew she was mistaken.

Dr. Moore's testimony both to the Naimark Review and the MAC was that research trial of L1 continued after both trials had been terminated. Yet the fact that both trials had been terminated, and neither continued, was well documented in records available to her. Thus the basis of her misunderstand-

ing is unclear. Dr. O’Brodivich relied on Dr. Moore’s incorrect information in his testimony both to the Naimark Review and the MAC.

Dr. O’Brodivich put forward allegations against Dr. Olivieri in the Naimark Review. The narrative set out in the Naimark Report follows in essential respects the one he put forward in his memo to Dr. Naimark dated September 24, 1998, in which he relied on Dr. Moore’s incorrect testimony. He cooperated with Dr. Koren in putting forward information against Dr. Olivieri during the Naimark Review, and HSC’s harassment investigator Ms. Humphrey “conclude[d] that in all likelihood that the memo [of September 24, 1998] was prepared with input from Dr. Koren.”³

Dr. Koren’s false allegations and testimony were believed. This bolstered the mistaken and incorrect information of Dr. Moore and Dr. O’Brodivich. In consequence, very serious adverse actions were taken against Dr. Olivieri and the L1 controversy was widened and prolonged. Dr. Koren’s conduct in these matters has not been addressed, even after he admitted to dishonest actions against Dr. Olivieri in a related context.

(2) Differential treatment

A salient feature of the L1 controversy is the difference between the treatment accorded to Dr. Koren and that accorded to Dr. Olivieri. The following are examples of such differential treatment.

1. The Hospital for Sick Children gave Dr. Koren’s views and conduct full and fair consideration, even when that conduct was improper. When he eventually admitted to misconduct and lying, he was provided with due process, and mitigating factors were taken into account. By contrast, the Hospital did not respect reasoned positions taken by Dr. Olivieri and wrongly cast her proper conduct as misconduct. The Hospital took very serious actions against Dr. Olivieri, in each instance without due process and in some instances precipitously. By contrast, when complaints of misconduct supported by substantial evidence were made against Dr. Koren, lengthy investigations followed. Although action was taken in some instances, in other instances we do not know of any action taken to date, and some complaints against Dr. Koren have not yet been investigated.
2. When in 1996 Dr. Olivieri identified a risk of Apotex’s drug L1 and Apotex attempted to prevent her from communicating on the risk, the Hospital framed this ethical issue as a scientific dispute: “The Hospital took the position that the conflict was a scientific controversy, that the peer-review process was best equipped to decide the issue.”⁴ In contrast, when the peer-reviewed medical literature supported a clinical practice of Dr. Olivieri—the use of liver biopsy as a guide to therapy for patients

with thalassemia major—the Hospital ignored this and relied instead on incorrect medical testimony of Dr. Koren, who is not an expert in this field. It consulted no independent experts. (See sections 5P and 5Q.)

3. The Hospital criticized and acted against Dr. Olivieri for an alleged “failure” to promptly report the second unexpected risk of L1 she identified to the Research Ethics Board (REB). Yet although Dr. Koren claimed, in writing, that he both knew of the risk and was the person responsible to report it, and the Hospital said that he told no one about this risk until he was asked about it by Dr. O’Brodivich, there has been no investigation or action regarding his “failure” in this matter. (See section 5O.)
4. The Hospital made public statements in which allegations against the quality of Dr. Olivieri’s work made privately to it by Apotex were repeated. It did this without investigation as to their validity and without first giving her an opportunity to respond. The Hospital’s public statement damaged her professional reputation. In contrast, after Dr. Olivieri and her colleagues provided extensive forensic evidence of serious misconduct by Dr. Koren in May 1999, and still more conclusive forensic evidence in December 1999, the Chair of the Board of Trustees urged them “not to take any unilateral steps which might damage the reputation of one of your colleagues.”⁵ (See sections 5L(8) and 5N(16).)
5. In 1997 and 1999 Dr. Koren published findings on the efficacy of Apotex’s drug L1 that were compatible with the position of Apotex, without disclosing the financial support he received from Apotex, and without giving credit to the contributions of Dr. Olivieri and others to generating the data. In a letter criticizing Dr. Olivieri that he submitted to the Naimark Review in 1998, Dr. Koren wrote that the second unexpected risk of L1 constituted “life threatening toxicity,” yet he made no mention of this risk in his 1997 and 1999 publications on L1, all of which were published after he was provided with a full report on that risk. We are not aware of any action taken by either the University or the Hospital in regard to such conduct by Dr. Koren. (See sections 5E, 5H, 5O and 5R(5).)

While the responsibility for some of these instances of differential treatment lies with the Hospital, the University must also bear responsibility for not addressing some of Dr. Koren’s academic and professional conduct, and for not yet holding him to the same standard as other faculty members.

(3) Dr. Koren's anonymous letters

The anonymous letters and the initial identification of Dr. Koren as the author. During the period mid-October 1998 to mid-May 1999 a series of five anonymous letters against Drs. Olivieri, Durie, Chan and Gallie was sent. The first contained allegations against Dr. Olivieri, and was faxed to the *Globe and Mail* newspaper on October 20, 1998. Several enclosures were faxed to the newspaper along with the anonymous letter, including several pages from a letter by Apotex Vice-President Dr. Spino to HSC President Mr. Strofolino and several paragraphs from the September 24, 1998 memo by Dr. O'Brodovich to the Naimark Review. The enclosures also contained or implied allegations against Dr. Olivieri. The second letter, dated October 21, was addressed to Dr. Durie. The letter said Dr. Durie had "caused HSC insurmountable damage," said he "should leave this institution," and called him "a British version of a foul air balloon [sic]." Dr. Durie was also the recipient of the third letter in the series, sent December 21. It called Drs. Olivieri, Chan and Gallie "unethical" and "a group of pigs." It asked Dr. Durie, "did you think that their shit won't touch you?" and suggested he "run as fast as [he] can." On February 24, 1999 a large number of HSC staff received a letter ridiculing Drs. Gallie and Olivieri. The last of the series was sent to Dr. Durie on May 14, and accused him of "contaminating our air and fabric" and suggested that the Hospital should have "let people like you go long ago."⁶

Dr. Durie *et al.* lodged complaints about each of the letters with HSC administrators, with the Board of Trustees and with HSC legal counsel, directly after each letter was received. After the fourth letter in the series, they also complained to Dean Aberman. The HSC administration sent out notices to staff that such letters constituted misconduct, but the author was not discovered and called to account.⁷

Drs. Chan, Durie, Gallie and Olivieri reported to us that they considered these letters to be attempts to discredit them and to intimidate them from continuing in their criticism of the conduct of Apotex, the Hospital and Dr. Koren, thereby infringing their academic freedom. The anonymous author clearly transgressed accepted standards of professional conduct. Dr. Chan *et al.* reported that they became increasingly concerned about what they felt was a lack of any effective response by the Hospital and the University to their complaints, so in the late winter of 1999 they hired a private detective who gathered information. They engaged forensic experts, a linguist and a documents expert, to review this information. The experts concluded that Dr. Koren was the author of the anonymous letters. The reports of the experts were enclosed with their written complaint against him submitted to the

Hospital and the University on May 17, 1999, and additional material was submitted in June 1999.⁸

The investigation for HSC by Ms. Humphrey. The Hospital discussed the complaint with Dr. Koren and he denied responsibility for the anonymous letters. The Hospital then hired its own investigator, Ms. Barbara Humphrey. The University left the investigation entirely to the Hospital and made no arrangement to have the Hospital's investigator consider whether Dr. Koren violated any University norms of conduct.⁹ Ms. Humphrey hired forensic experts who, among other things, essentially duplicated the work of those Dr. Chan *et al.* had hired. They reached the same conclusion.¹⁰

During Ms. Humphrey's investigation, Dr. Koren put forward several accounts about the origin of the anonymous letters, including naming a specific individual as having written them rather than himself. Ms. Humphrey examined these accounts in detail and concluded that "on the balance of probabilities" they were false.¹¹ Many months went by and Ms. Humphrey still had not completed her investigation, due in part, she reported, to Dr. Koren's attempts to "frustrate" her inquiry through lying.¹²

In early December 1999, seven months after they had submitted the first forensic evidence, Dr. Gallie *et al.* obtained DNA evidence that Dr. Koren was the author. The matching DNA was from envelopes of two of the anonymous letters, and from the hand-addressed envelope that contained a hand-written letter, in Dr. Koren's handwriting, that he had sent to Dr. Michèle Brill-Edwards (see section 5U(6)).* Dr. Gallie *et al.* provided this new forensic report to the University and the Hospital on December 8 and Ms. Humphrey received a copy on December 10. Dr. Koren was informed of this development on or about December 10. Subsequently, he admitted to responsibility for the anonymous letters and, by implication, to having lied persistently to cover this up. Following his admission, Ms. Humphrey's report was completed, on December 20. (See also sections 5N(16) and (17).)

Ms. Humphrey did not rely on the DNA evidence provided by Dr. Gallie *et al.*. She said that it had been put forward by an interested party, and that the DNA evidence "would not, even if we relied on it, alter the conclusion arrived at by this Investigator."¹³ Ms. Humphrey had earlier asked Dr. Koren for a saliva sample, but he had refused to provide one. Her report found that Dr. Koren had "provided false and misleading information," and that he was "the

*The DNA report, from Helix Biotech of Richmond, B.C., and dated December 7, 1999, identified the author of the three samples (two anonymous, one known) as the same male person, with a frequency of "1 in 385 billion in the North American Caucasian population," with similar frequencies for other North American populations.

individual who drafted and disseminated” all five of the anonymous letters.¹⁴ She based the latter finding on “strong forensic evidence,” much of which was similar to that already provided by Dr. Gallie *et al.* in May 1999. Her report stated that she also found “compelling motive evidence,” including the fact that Dr. Koren had been criticized by Dr. Gallie *et al.* for his support of the position of Apotex on its drug L1.¹⁵ Ms. Humphrey noted that the anonymous letters were:

directed at attacking and impugning the professional status, competency and reputation of Dr. Olivieri, Dr. Durie and to a lesser extent Dr. Gallie and Dr. Chan.¹⁶

Ms. Humphrey concluded that Dr. Koren had violated Hospital policy and breached the “trust attending the positions of leadership and direction that Dr. Koren occupies.”¹⁷ Somewhat surprisingly, the course of action she recommended was that “the HSC give serious consideration to a mediation process”¹⁸ involving Dr. Koren and the victims of his series of letters. Dr. Gallie *et al.* reported to this Committee that the facts that the Hospital had retained Ms. Humphrey to investigate harassment and provide advice, and that this advice did not treat Dr. Koren’s misconduct and breach of trust as necessitating more than a mediation process, heightened their concerns about the Hospital’s intentions with respect to Dr. Koren, and with respect to themselves. They reported that they were not reassured by the article written by Mr. Alexander Aird, Chair of the Hospital’s Board of Trustees in the *Globe and Mail* on December 31, 1999, in which he said that Dr. Koren “has admitted to authoring unwanted anonymous mail.” This was a curious description for letters in which Dr. Koren called his colleagues “pigs” and “unethical,” where one letter purporting to be from a number of colleagues said, “you cannot overestimate the contempt, appaul [sic] and mistrust we have towards you,” and another suggested that Dr. Durie should have been “let go” by the Hospital “long ago.” Mr. Aird’s article then quoted a passage from Ms. Humphrey’s report in which she suggested that the victims of Dr. Koren’s anonymous harassing mail bore some responsibility for “a web of conflict” in which Dr. Koren had become enmeshed. Mr. Aird’s article omitted mention of the fact that Dr. Koren’s admission was preceded by seven months of lying, and came only after he had been identified by DNA evidence.

Ms. Humphrey’s recommendation of “a mediation process” to address serious misconduct and dishonesty by Dr. Koren, and Mr. Aird’s characterization of the misconduct by Dr. Koren as innocuous, were factors diverting attention away from a process that had been ongoing for several months. The new Dean of Medicine, Dr. Naylor, had brought a complex mediation process between Drs. Chan, Dick, Durie, Gallie and Olivieri, and the Hospital, covering a range of issues, to near completion in early December

1999. However, as discussed in section 5.N(16), apprehensions that the Hospital would not properly address the serious misconduct and dishonesty to which Dr. Koren had just admitted, resulted in Dr. Chan *et al.* deciding in December to defer signing the Dean's mediation proposal. Mr. Aird's public statement at the end of December contributed to a decision to defer signing for a longer period. Dr. Olivieri and her colleagues reported to us that they were concerned that failure to address such serious harassment and dishonesty would mean that the benefits to them set out in the mediation document could be nullified by a continuation of abusive conduct by Dr. Koren. If his improper conduct were not properly addressed, they felt it would mean that those in authority had a high level of tolerance for his misconduct. They felt this would provide a context in which Dr. Koren's attempts to create circumstances in which they would "leave this institution" would be more successful.¹⁹

(4) Disciplinary proceedings against Dr. Koren

On December 21, after Dr. Koren admitted to writing the anonymous letters and the day on which articles in the *Globe and Mail* and the *National Post* suggested he was the author,²⁰ the University and the Hospital both suspended him with pay, pending disciplinary proceedings.²¹ The disciplinary panel included senior officers of the University and Hospital, and the proceedings extended over several months. In addition to Ms. Humphrey's recommendation of mediation, the panel had available the submissions of Drs. Chan, Dick, Durie, Gallie and Olivieri, and the University of Toronto Faculty Association (UTFA) to the effect that Dr. Koren's conduct warranted dismissal. In support of their position, Dr. Chan *et al.* and UTFA presented additional allegations and information on related misconduct. Dr. Koren was accorded due process: he was represented by legal counsel; he was provided with access to the Humphrey report and to the allegations and testimony by Dr. Chan *et al.* and UTFA; and he had the opportunity to respond.²²

Disciplinary action was imposed four months later, on April 11, 2000. In a joint letter to Dr. Koren, President Prichard of the University and President Strofolino of the Hospital, listed the actions taken and the reasons. The actions were announced to the press on April 14 and details of the Presidents' letter were later published by the *Toronto Star* and *Nature Medicine*.²³ The Presidents cited three types of misconduct: "disseminating anonymous harassing correspondence;" denial of involvement to the Hospital, the University and Ms. Humphrey; and "late admission of responsibility."²⁴ They noted that he had thrown away a computer and thereby "might have destroyed the

evidence that could have proved or disproved” allegations of further misconduct by him.²⁵

In their disciplinary letter the Presidents wrote to Dr. Koren that:

Academic freedom cannot flourish in an environment in which unwarranted attacks are made on colleague’s personal and professional integrity. Anonymously writing and communicating offensive allegations to colleagues demonstrates a complete disregard for colleagues and for the values which the Hospital and the University seek to foster. The Hospital and the University have the right to expect that their physicians and clinical faculty members will co-operate and be truthful. Your conduct in lying to the Hospital, to the University and to the investigator went beyond a failure to cooperate. You intentionally obstructed the Hospital’s investigation.

You occupy a position of great trust. You have great responsibilities. Your conduct in sending the anonymous letters and in repeatedly lying to Ms. Humphrey demonstrates lack of fair and ethical dealing with colleagues, irresponsibility and reckless dereliction of duty. Your misconduct was hurtful to your colleagues. You did not act in good faith. You only admitted misconduct after incontrovertible evidence was obtained. Your admission was too late. You did not tell the truth when you felt untruth would serve you better. Your lying triggered an expensive investigation. You abused the trust reposed in you and you failed to live up to your responsibilities.

You have provided no acceptable explanation for your misconduct. *Your actions constitute gross misconduct and provide sufficient grounds for dismissal.*²⁶ (emphasis added)

However, the Presidents did not dismiss Dr. Koren. They took into account several “mitigating factors,” that were outlined in their disciplinary letter. These included: his accomplishments “as a researcher;” his “recent MRC Senior Scientist Award;” that he had no record of previous disciplinary action; and “an outpouring of sympathy for you from your colleagues.” They also noted that he had resigned from two administrative posts. Instead of dismissal, their April 11, 2000 letter imposed: a continuation of Dr. Koren’s suspension until June 1, 2000, the last two months without pay; immediate removal from the CIBC-Wood Gundy Children’s Miracle Foundation Chair in Child Health Research; removal from a University administrative position; and a \$35,000 fine “as partial restitution” for the cost of Ms. Humphrey’s investigation.²⁷

Presidents Prichard and Strofolino added that:

This suspension will be on your record. Should there be any other misconduct resulting in discipline to you, your record of discipline will be taken into account in deciding the proper penalty for such other misconduct. In the event that the current research misconduct proceedings result in discipline, or should further information come to light concerning the two letters dated December 18, 1996 and February 8, 1997 that results in a finding of

misconduct, any discipline for such misconduct would take into account this suspension.²⁸

It is of note that the two Presidents imposed disciplinary action only for the conduct to which Dr. Koren admitted, “We have based our decision on the admitted misconduct referred to above [writing and sending the anonymous letters, lying about this, and late admission of responsibility].”²⁹ The Hospital and the University did not fully investigate “the two letters” (see section 5R(6)).

At the time this report was completed we had no information on whether any action was taken against Dr. Koren as a result of any investigations into possible “research misconduct,” or other possible misconduct by Dr. Koren. In the following subsections we discuss evidence which has led us to conclude that he has committed misconduct for which he has not, to our knowledge, been called to account.

(5) Dr. Koren’s 1999 journal article on L1

In 1999 Dr. Koren published an article on the efficacy of Apotex’s drug deferiprone (L1) in the treatment of iron-loading in thalassemia patients. He was senior author and two Apotex-funded research fellows he supervised, Drs. Orna Diav-Citrin and Gordana Atanackovic, were co-authors, with Dr. Diav-Citrin listed as first author. The article was published in the journal *Therapeutic Drug Monitoring*, and reported data from the long-term trial of L1 (LA-03), that began in 1989 as a pilot study and continued until May 1996 when it was terminated by Apotex. The article was titled “An Investigation Into Variability of the Therapeutic Response to Deferiprone in Patients With Thalassemia Major,” and it used data on hepatic iron concentrations (HIC) and on plasma vitamin C (ascorbic acid) concentrations of trial participants, in addition to pharmacokinetic data.³⁰

During the LA-03 trial, the HIC data was generated primarily by Dr. Olivieri in collaboration with Dr. Douglas Templeton (Department of Clinical Biochemistry, University of Toronto), and (from 1992 onward) Dr. Brittenham, some from biopsy specimens, and some from SQUID measurements performed in Dr. Brittenham’s laboratory. Also during the LA-03 trial, Dr. Olivieri collaborated with Dr. Robert Jacob (United States Department of Agriculture) who made determinations of plasma vitamin C concentrations in his laboratory.* (See section 5A.)

*The possible relevance of plasma ascorbic acid concentrations to the study of efficacy of an iron-chelation treatment is outlined in the LA-05 protocol proposal prepared by Dr. Olivieri in September 1995. This proposed a detailed methodology for studying the etiology of the loss of sustained efficacy of L1 observed in some LA-03 participants, and ascorbic acid was included as

The 1999 article by Drs. Diav-Citrin, Atanackovic and Koren stated the conclusion:

This study confirmed the effectiveness of deferiprone in heavily iron-loaded [thalassemia] patients and provided evidence that its effectiveness decreases in proportion to liver iron load.³¹

A new element of the L1 controversy had developed in the spring of 1997, when it became known that Dr. Koren was senior author of two abstracts on LA-01 and LA-03 data presented at a conference on thalassemia in Malta, of which the first author was an Apotex employee, as discussed in section 5N(5). (Drs. Diav-Citrin and Atanackovic also were co-authors of both these abstracts.) In mid-April 1998 there was further controversy when Dr. Diav-Citrin accessed a patient's chart in the HSC thalassaemia clinic, and Dr. Olivieri lodged a complaint with Medical Advisory Committee Chair Dr. Becker that the access was unauthorized (see section 5L(6)). Dr. Koren then wrote to Dr. Becker concerning the research activities he and his Apotex-funded research fellows had been conducting after the May 1996 termination of the trials of L1 in thalassemia:

... we have not participated in any effort by Apotex to develop the drug for thalassemia after the trial. All our efforts focus on the use of deferiprone in acute iron poisoning [in an animal model].... The funding we received [from Apotex] after the discontinuation of the trial ... was not dependent on work related to deferiprone in thalassemia.³²

However, a month later, on May 11, in another letter written in connection with the controversy over access to clinic charts, Dr. Koren acknowledged in writing that Dr. Diav-Citrin and he had been working on a paper on L1 in thalassemia. In this letter Dr. Koren gave another account of activities "since the termination of the trials,"³³ in particular:

The study Dr. Orna Citrin is completing under my supervision pertains to pharmacokinetic data collected on patients between 1989 and Mid 1995... Our study... has nothing to do with Apotex ...³⁴

The time period (1989 onward) makes it clear that this was data from the long-term trial (LA-03). In a follow-up note on May 14, 1998 Dr. Koren added:

After May 1996 I switched Orna's research focus from L1 to other areas of pharmacology and she started writing up the pharmacokinetics aspects of L1. These were presented in 97-98 meetings.³⁵

An abstract published by Drs. Koren, Diav-Citrin and Atanackovic in February 1997 indicates that, in fact, they were working on a broader analysis of the efficacy of L1 based on LA-03 data, using not only

one of several factors to be assessed. (See section 5D.) The LA-05 protocol was never approved or implemented because Apotex did not agree to sponsor such a trial of its drug L1.

pharmacokinetics but also HIC and plasma vitamin C data of patients who had been in that trial.³⁶

In a handwritten note written on May 14, 1998, Dr. Koren recorded details of a meeting he and Dr. Diav-Citrin had the day before, May 13, with Drs. Spino and Tricta of Apotex “to discuss Orna’s paper.”³⁷ It is reasonable to conclude that this discussion was about the article Drs. Koren, Diav-Citrin and Atanackovic subsequently published in *Therapeutic Drug Monitoring* in 1999, because Dr. Koren’s note referred to “SQUID and biopsy data,”³⁸ that is, data on HIC, the principal measure of efficacy in the LA-03 trial and the focus of the 1999 article. (Dr. Koren’s record of the discussion says nothing about any study of acute iron poisoning in an animal model.) The note records a disagreement on a point of methodology between the authors and the Apotex representatives, but it does not record any disagreement on findings or conclusions. The note ends with a comment that Drs. Koren and Diav-Citrin decided to submit the article for publication.

The published article says that it was received by the journal on August 12, 1998 and accepted for publication on October 6, 1998. It reports data of nineteen thalassemia patients who had been enrolled in the LA-03 trial and says:

For the sake of this analysis, data entry ended in the middle of 1995.³⁹

Data entry for this trial continued into 1996, but the article does not explain why data points collected later than the middle of 1995 were not included in its analysis of efficacy of the drug. As noted in section 5D, it was in the middle of 1995 that Dr. Olivieri began withdrawing a significant number of these nineteen patients from the trial and transferring them to standard therapy, because their most recent HICs indicated loss of sustained efficacy in their individual cases to an extent that they were at risk from iron overload.

The following facts regarding the 1999 article are clear on reading it:

- The article does not disclose that Apotex funded the work of the three co-authors.
- The article does not acknowledge the contributions of Drs. Olivieri, Brittenham, Jacob, and others to generating the data reported in it.
- The article does not mention the risk of progression of liver fibrosis identified by Dr. Olivieri in data of the same cohort of patients, even though Dr. Olivieri had fully apprised Dr. Koren of this finding in early February 1997 and she had published the finding in 1997 abstracts and in a 1998 article in the *New England Journal of Medicine*.

The absence of any reference to the previously published finding that L1 poses a risk of progression of liver fibrosis is of particular note, because in Dr. Koren’s testimony to the Naimark Review he characterized the risk as one of “life-threatening toxicity” (his letter is reproduced in full at page 41 of the Naimark Report). After reading the article, we asked each of Dr. Olivieri and Dr. Brittenham whether they had been given any notice of, or opportunity to review or participate in, the publication. Each replied that they had been given no such notice or opportunity.

We conclude that the conduct of Drs. Koren, Diav-Citrin and Atanackovic in this publication, especially the conduct of Dr. Koren, the senior author and research supervisor of the other two authors, was not in conformity with widely accepted standards of conduct in scientific publication, and specifically not in conformity with policies of the University of Toronto.⁴⁰

(6) Dr. Koren's signed letters against Dr. Olivieri

Dr. Koren put forward to the Naimark Review two letters signed by him and addressed to Dr. Olivieri, dated December 18, 1996 and February 8, 1997. These were taken to be authentic and reproduced in full at page 41 of the Naimark Report. Dr. Olivieri reported that she had never received these two letters and knew nothing of them until the Naimark Report was published. During the disciplinary proceedings against Dr. Koren for his anonymous letters, Drs. Olivieri, Chan, Dick, Durie and Gallie, and the UTFA alleged that these two signed letters constituted additional misconduct by Dr. Koren. In their April 2000 disciplinary letter to Dr. Koren, Presidents Prichard and Strofolino summarized the allegation:

The allegation of misconduct that you deny and that remains troubling to the institutions is that you prepared "two false letters" for submission to Dr. Naimark. These letters are dated December 18, 1996 and February 8, 1997 and are addressed to Dr. Nancy Olivieri and are signed by you.... The allegation is that the letters were prepared at a later date to buttress your submission to the Naimark inquiry and thereby discredit Dr. Olivieri.⁴¹

There were two aspects to this allegation: (i) that the dates of the two signed letters were false; (ii) and that their contents were false. The December 20, 1999 report of Ms. Humphrey also raised questions about the authenticity of these letters, which she had considered as comparisons for the anonymous letters. Ms. Humphrey reported that physical examination of the paper on which these letters were typed suggested they may have been typed much later than the dates given on them.⁴² She also reported that during her inquiry Dr. Koren had alleged that a part-time employee of his had typed certain letters, including these two signed letters. Ms. Humphrey interviewed this person and the person said she had typed both signed letters. After forensic examination, Ms. Humphrey concluded that the testimony by Dr. Koren and the testimony by his part-time employee on these signed letters (and on related matters) were "inconsistent and contradictory," and "neither credible nor feasible."⁴³

The presidents' disciplinary letter did not address the contents of the letters, even though the Naimark Report relied on the contents, as well as on the "dates" of the two letters. As for the "dates:"

The two institutions investigated this allegation to endeavour to determine whether the letters had been prepared on the dates shown and sent to Dr. Olivieri as stated by you. ... In throwing away the computer on which you typed these letters, you might have destroyed the evidence that could have proved or disproved this allegation. As a result of your action, we are unable to make a conclusive determination at this time. Should further evidence come to light concerning the authenticity of these two letters, the matter will be revisited. The case on this allegation is not closed.⁴⁴

Presidents Prichard and Strofolino did not explain why they did not investigate the contents of the two letters. Unlike the dates, the assessment of the contents was not dependent on retrieval of a discarded computer—copies of the two letters are in the HSC library archives, and the Naimark Review reproduced both of them in their entirety in the main body of its Report.⁴⁵ As discussed in section 5.O.2, the contents of these two letters are contradicted by documents written by Dr. Koren himself, as well as by other documents.

(7) Dr. Koren’s incorrect & false testimony

In this subsection, we summarize the main allegations by Dr. Koren against Dr. Olivieri, some put forward both to the Naimark Review and to the MAC inquiry, and others put forward to the MAC inquiry.⁴⁶ Documents showing that the allegations were incorrect were included in the collections of documents available to these inquiries, yet they believed his allegations. Dr. Koren also made some of these allegations in Ms. Humphrey’s investigation. The allegations centred on identification and reporting of the risk of progression of liver fibrosis that Dr. Olivieri identified in early February 1997 in data of one group of patients, and on her clinical actions to assess whether patients in another group had experienced this adverse effect.

a) Dr. Koren alleged that he was the practitioner for the post-trial Emergency Drug Release (EDR) use of L1, and that in consequence it was he who had the responsibility to report any adverse drug reactions (ADR) to Health Canada and to Apotex, under the *Food and Drugs Act* and *Regulations*. He also alleged that Dr. Olivieri had an obligation to report any ADR to him, so that he could fulfill his alleged reporting obligations.⁴⁷ In testimony to the MAC, Dr. O’Brodivich also put forward the allegation that Dr. Olivieri had responsibilities to advise Dr. Koren of adverse effects.⁴⁸

However, Dr. Koren was not the practitioner. The practitioner was Dr. Olivieri, the treating physician of the patients. Even Dr. Koren acknowledged this on page 5 of his December 1998 letter to the MAC, where he wrote that, “Dr. Olivieri refused to give Apotex immediate details of her suspicions and proofs of serious toxicity, despite clear regulations by Health Canada.”⁴⁹ In other words, he himself stated in the same letter that the reporting requirements applied to Dr. Olivieri as the practitioner under the *Act* and *Regulations*, not to him. He thereby contradicted his allegation made on pages 1 and 2 of that letter. On page 1 he wrote that it was he who had the obligation to “report it [any adverse drug event] to the company and to the government, according to Health Canada Regulations.” On page 2 he wrote, “I was... the individual responsible for Emergency Drug Release... I believe it was her obligation to share the serious suspicion of hepatic

toxicity, so I could report it to Health Canada.” In fact, Dr. Olivieri did report this risk to Apotex and to Health Canada, as she was legally required to do as the practitioner.

b) Dr. Olivieri was not required to report the risk to Dr. Koren, but she nevertheless sent him a copy of the complete report on the risk, on February 5, 1997, one day after she sent it to Apotex. Although he had thus received the full report, Dr. Koren told no one about this risk until two weeks later, when he was asked about it by Dr. O’Brodivich. Thus, Dr. Olivieri did report the risk to Dr. Koren (though she was not obligated to do so), and he, who later alleged that it was he who had the responsibility to report it to Health Canada and others, reported it to no one. Yet he gave testimony to the MAC that he had not been informed of the risk.

c) Dr. Koren gave conflicting accounts of when and how he came to be informed of the risk of progression of liver fibrosis. On February 19, 1997, Dr. Koren told Dr. O’Brodivich that he did have a copy of Dr. Olivieri’s report, but that he had received it from Apotex (as Dr. O’Brodivich related in a letter dated March 3, 1997 to Dr. Olivieri’s CMAA lawyer, Mr. Colangelo). Therefore, Dr. Koren knew that Dr. Olivieri had reported full details of the identification of the risk to Apotex, contrary to his allegation to the MAC that she did not report her “proofs” of the risk to the manufacturer.

Dr. O’Brodivich (in his letter to Mr. Colangelo) implied, and the Naimark Report (p. 134) said that Dr. Olivieri had given Dr. Koren no information “until inquiries were made of her” on February 19, 1997. Dr. Koren told the MAC on January 19, 1999 that he “had not been advised” by Dr. Olivieri.⁵⁰ This account of Dr. Koren to the MAC is consistent with what Dr. John Dick reported that Dr. Koren told him in September 1997, namely, that “he [Dr. Koren] only found out about it when [on February 19] Hugh [Dr. O’Brodivich] showed him the letter [Dr. Olivieri’s letter to the regulators].”⁵¹ However, Dr. Koren’s accounts—to Dr. Dick he said he first obtained the report from Dr. O’Brodivich, but to Dr. O’Brodivich he said he first obtained the report from Apotex. In fact, Dr. Koren actually obtained the report from Dr. Olivieri “in early February,” as he acknowledged to Ms. Humphrey during her investigation.⁵² One of the signed letters by Dr. Koren reproduced in the Naimark Report (p. 41) indicates that he received the report on the risk on or before February 8, 1997.*

*As discussed above, the fact that Dr. Koren typed the date of “February 8, 1997” on this letter does not establish his claim that he wrote the letter on that date. Rather, it indicates an acknowledgement that on or about that date he did indeed receive Dr. Olivieri’s report on the risk, as he acknowledged to Ms. Humphrey in 1999. Since Dr. Olivieri had sent the report to him through their joint counsel on February 5, 1997, if he had actually written the letter during the

d) In Ms. Humphrey’s investigation, Dr. Koren repeated the claim he had made to the Naimark Review and the MAC that he was the practitioner for the EDR treatment arrangement. Ms. Humphrey reported that he told her that, “he [Dr. Koren] was responsible for those kids and he had promised to let the Company [Apotex] know and let Health Canada know of any adverse effects.”⁵³ However, aside from the facts that he was informed of full details of the identification of the risk (on or shortly after February 5, 1997) and did not let anyone know about it, he wrote letters and memos in 1997 and 1998 confirming that he was *not* responsible for “those kids.” Indeed he wrote that, after the trials were terminated in May 1996, he had no involvement with the monitoring of any of the patients on L1. There were two groups of patients treated with L1 under EDR, some from the former LA-01 cohort and some from the former LA-03 cohort. With respect to the patients who had been in the LA-01 cohort, Dr. Koren wrote in August 1997 that, after May 1996, “I... was not part of the collection, analysis or interpretation of the data” arising from the monitoring of patients.⁵⁴ With respect to the patients who had been in the former LA-03 cohort, Dr. Koren wrote in May 1998 that after the trial termination, he “was not involved any more in data collection and was not aware that data were continuously collected.”⁵⁵

e) In May 1998, in connection with the controversy of Dr. Diav-Citrin’s access to charts in the thalassemia clinic, Dr. Koren said that he was unaware that patients who continued on L1 were monitored for hepatic iron concentration (HIC). In a memo to Dr. Buchwald dated May 14, 1998 he outlined Dr. Diav-Citrin’s activities with respect to patients in the former LA-03 trial cohort during the close-out period in 1996, closing with the statement that:

These activities were in the context of compassionate drug administration [EDR] after discontinuation of the [LA-03] trial, and we were not aware that Dr. Olivieri continued to monitor study endpoints, and especially liver iron.⁵⁶

However, Dr. Koren did know that Dr. Olivieri continued to monitor patients using “study endpoints”—specifically, he knew she continued to monitor liver iron (HIC), the only accurate measure of efficacy of any iron chelation treatment. First, on July 15, 1996 Dr. Koren himself co-signed a letter with her in which they expressly stated that a patient would only be treated with L1 under EDR by Dr. Olivieri if the patient agreed to be monitored by the same safety tests as in the terminated trials, and this letter expressly included “liver biopsy,” the purpose of which was to monitor HIC, as well as histology.⁵⁷ In this joint letter, Drs. Olivieri and Koren stated that

Naimark Review in 1998 to buttress his submission to that Review, as Dr. Olivieri alleged, choice of the date “February 8, 1997” would help to lend an air of authenticity to the letter.

they remained concerned that L1 “may not have optimal efficacy,” which could expose patients to the risks of iron loading. It was for this reason that “liver biopsy” for HIC and histology was specified in their letter.

Second, Dr. Koren knew that patients who continued on L1 under EDR had in fact been monitored after July 1996, by HIC and other tests. In his May 14, 1998 memo to Dr. Buchwald he acknowledged that “Orna [Dr. Diav-Citrin] indeed continued to see patients to monitor those who received the drug on a compassionate basis [EDR] until the end of November 1996.”⁵⁸ On October 28, 1996 Dr. Olivieri wrote to Dr. Koren about the second stoppage in the L1 supply by Apotex, and in this letter she noted an account she had received that Apotex had taken this action because it objected to her monitoring of the patients and then possibly reporting the results of the monitoring (see section 5J(3)). Dr. Koren was copied on the report of close-out data from both trials that Dr. Olivieri sent to Apotex on November 15, 1996. This report included data points, including HIC, collected until late October 1996.⁵⁹ Dr. Spino wrote to Dr. Koren on October 23, 1997 requesting assistance in obtaining source data of both the LA-03 and LA-01 patient groups. Dr. Spino specifically asked for “histological assessments of the biopsy samples” and “All *iron assessments since May 1996*, reported by date, and whether the result was obtained by biopsy or SQUID.”⁶⁰ (emphasis added) That Dr. Koren read and understood Dr. Spino’s request in this letter is clear from letter Dr. Koren sent to Dr. O’Brodivich on November 3, 1997, to the effect that he was unable to assist Apotex in gaining access to this data, because he himself had not been involved in the monitoring of patients after May 1996.⁶¹

f) Dr. Koren put forward testimony to the MAC that a research trial of L1 had continued after Apotex terminated both trials. Yet documents show very clearly that he knew Apotex had terminated both trials and that there was no trial of L1 after May 1996.* He could have corrected the misunderstandings of Dr. Moore and Dr. O’Brodivich on this central point. Instead of doing so, he put forward to the MAC in quotes the incorrect statement by Dr. Moore that the long-term trial had continued.

*Dr. Koren had received the notice from Apotex on May 24, 1996 that both trials had been terminated, and he was present in Dean Aberman’s mediation meeting on June 7, 1996 in which Apotex refused to reinstate any trial (but agreed to the non-trial EDR arrangement). Dr. Koren signed two letters, jointly with Dr. Olivieri, to Dr. Haslam on May 25, 1996 and to Dr. Zlotkin on July 15, 1996, stating that both trials had been terminated. In 1997 and 1998 he wrote several letters confirming that both trials had been terminated. For instance, in a letter to Dr. Buchwald on May 11, 1998, Dr. Koren wrote of “the termination of the trials in May 1996.” (See sections 5K and 5P for citations of this and other letters to the same effect.)

g) Dr. Koren put forward testimony to the MAC that liver biopsies arranged by Dr. Olivieri during February-April 1997 were not clinically indicated. These were on some patients receiving L1 who had biopsies after the risk of progression of liver fibrosis had been identified. In fact these biopsies were clinically indicated (see sections 5K and 5Q), and this was clear from documentation in Dr. Olivieri's report on the risk, two copies of which Dr. Koren himself said he received. He also alleged that liver biopsy was "a potentially life threatening procedure." He likely knew that this was not an accurate characterization, because the information and consent forms for patients enrolling in the long-term trial explained that it was a procedure with very low risk. As an investigator for that trial (1989–1996), Dr. Koren was responsible for the accuracy of these information and consent forms. (See section 5Q.)

(8) Conclusions

- 1** | Dr. Koren put forward incorrect allegations and testimony against Dr. Olivieri to the Naimark Review and the MAC inquiry. His conduct ranged from at best seriously neglectful (for instance, in his allegations and testimony pertaining to liver biopsies), to clearly dishonest (for instance, in the allegation that Dr. Olivieri had not informed him of the risk of progression of liver fibrosis, and in the testimony that a trial of L1 continued after May 1996).
- 2** | Much of the L1 controversy from late 1998 onward has resulted from the incorrect and false testimony against Dr. Olivieri by Dr. Koren, and the apparently uncritical acceptance of his testimony by the Naimark Review and the Medical Advisory Committee.
- 3** | Dr. Koren's conduct in publishing the 1999 article on the efficacy of L1 in Therapeutic Drug Monitoring was not in conformity with accepted standards of conduct in regard to scientific publication.
- 4** | To our knowledge, neither the University of Toronto nor the Hospital for Sick Children has addressed the serious misconduct by Dr. Koren we have reviewed here, other than that pertaining to his authorship of the anonymous letters and his lying to conceal responsibility for them.

5S | Involvement of the CAUT and the UTFA

(1) Initial Involvement

ACADEMIC FREEDOM is a central issue in this case. So it is interesting that during the first two years of the L1 controversy (summer 1996 to summer 1998) none of those directly involved appear to have used the term academic freedom. Dr. Olivieri considered that she had a right to communicate her findings, senior HSC administrators agreed this was important, and Dean Aberman of the Faculty of Medicine considered Apotex's legal warnings a sufficient infringement of her right to communicate that he intervened to ask the company to desist. Yet neither they nor colleagues such as Dr. John Dick and Dr. Robert Phillips who intervened to try to resolve matters appear to have used the term academic freedom until the fall of 1998. This may be a reflection of the fact that many clinical professors of medicine are not involved in the activities of faculty associations. Those attempting to assist Dr. Olivieri in various ways, including her CMPA legal counsel and Dean Aberman, appear not to have advised her that academic freedom was a fundamental right that the University of Toronto was obligated to protect, encoded in University policies and enforceable under the University grievance procedure. She was not informed by administrators or colleagues that the Canadian Association of University Teachers (CAUT) and its local affiliate, the University of Toronto Faculty Association (UTFA), could be consulted for advice and possible assistance, despite the fact that faculty associations have provided advice and assistance to clinical professors in the past and continue to do so. After the controversy became widely publicized, academic freedom was a term employed by many to characterize aspects of the dispute.¹

Both CAUT and UTFA reported to us that they first learned of the case when major media outlets began covering it in mid-August 1998. CAUT became sufficiently interested to contact Dr. Olivieri for an interview and UTFA for additional information. The lead article in the September 1998 issue of the monthly *CAUT Bulletin* said that the case involved "academic freedom and research ethics," and that many scientists and physicians in HSC were calling for an inquiry.² When contacted by CAUT for information, UTFA had in turn contacted Dr. Cecil Yip, a former Grievance Vice-President of UTFA and now Vice-Dean (Research) of the Faculty of Medicine. Immediately thereafter, UTFA Grievance Vice-President Dr. Rhonda Love and UTFA General Counsel Ms. Allison Hudgins were invited to meet with University Provost Dr. Adel Sedra and Vice-Provost Dr. Paul Gooch for a two-hour briefing.³ Ms. Hudgins reported to us that the administrators said that the dispute was a Hospital matter, and that no University policies had been violated.⁴ Around this time (late August or early September), possibly as a result of her interview by the *CAUT Bulletin* reporter, Dr. Olivieri

telephoned Dr. Love, who offered to meet.⁵ However, neither followed up on this conversation.

Neither CAUT nor UTFA took further action in the matter until late November 1998.⁶ This lapse is hard to understand, since the *Bulletin* article had clearly identified academic freedom and research ethics, two principal concerns of CAUT and its affiliates, as being at the heart of the matter. In interviews with this Committee of Inquiry, representatives of both associations said they had no formal request for assistance and Dr. Olivieri had not taken up UTFA's offer to meet. However, Dr. Olivieri was by this time under great pressure from several quarters and did not clearly understand what advice or assistance the associations might have been able to provide. UTFA representatives said that they had accepted assurances by the Provost and Vice-Provost to the effect that the matter need not be of concern. However, it is common for administrators to have a different perspective on a dispute than faculty members. The usual practice of faculty associations in cases of dispute is to make wider inquiries with knowledgeable persons on both sides. In the present instance, this was not done. Representatives of both UTFA and CAUT told us they were constrained from prompt action by existing policies. Subsequently, however, both associations found ways to overcome the perceived constraints, became actively involved in the case, and invested very substantial resources. They have acknowledged that, in hindsight, they should have acted earlier.

Dr. John Dick and representatives of UTFA and CAUT told us that it was a former president of UTFA, Dr. Harvey Dyck, who persuaded UTFA and CAUT that they had a responsibility in this matter. Dr. Dyck also advised Dr. Dick and Drs. Chan, Durie, Gallie and Olivieri that they should approach these associations for advice and assistance. This occurred in late November 1998, and UTFA and CAUT both agreed to take up the case.

On November 24, 1998, CAUT issued a press release critical of the Naimark Review process which, by then, was nearly completed. The press release spoke for the Council of CAUT (which happened to be in its semi-annual meeting), including UTFA, and called upon the Hospital and the University "to stop this flawed review immediately and replace it with a proper, independent review."⁷ There was nothing that would have prevented CAUT from expressing the same view two months earlier, when it would have been more likely to have had practical effect. Indeed several prominent citizens from Toronto and elsewhere had already made similar representations to the Hospital and the University in September 1998.⁸

It is relevant to note that the practice of CAUT and its member associations has always been to seek fair adjudication processes for individuals who

bring complaints which, *prima facie*, have substance. Faculty associations normally do not take a position on the specific merits of the case until after a thorough investigation indicates they should. The November 1998 CAUT press release did not take a position on the merits of Dr. Olivieri's case, but rather expressed the view that the Naimark Review process was flawed.

Employee organizations like UTFA and CAUT are often, necessarily, confined to a reactive role in relation to actions by employers. However, a reactive role can still be effective, especially when timely, as events of January 1999 show (see sections 5M and 5N). Had UTFA and CAUT urged the University and the Hospital in late August or early September to establish a review constituted so as to attract participation by all parties, events might have developed in a different way.

(2) Subsequent involvement

Drs. Olivieri, Chan, Dick, Durie and Gallie became members of UTFA in late 1998 and the Association assisted them in lodging grievances under the University procedure. In January 1999, as a result of HSC's summary removal of Dr. Olivieri from her position as Director of the Hemoglobinopathy Program, CAUT and UTFA became intensively involved. Both organizations remained involved after the resolution agreement of January 25, 1999, when it became clear that significant issues remained outstanding and still others arose. (See sections 5M and 5N.)

An important matter not covered by the January 1999 agreement was the Medical Advisory Committee (MAC) inquiry into Dr. Olivieri's conduct. This proceeding, by the body that advises the Board of Trustees on such matters as hospital privileges and staff discipline, could potentially have resulted in serious damage to Dr. Olivieri's career. In early January 1999 the Hospital had denied due process to Dr. Olivieri in removing her from the directorship, and had issued an improper directive infringing her academic freedom, facts that the University, UTFA and CAUT had acknowledged at the time (see section 5M). All three can therefore reasonably be said to have had a responsibility to make representations to the Hospital Board requesting that such unfairness not be a factor in the MAC proceeding, but we have no evidence that any of them did so. It was the direct responsibility of the Hospital Board to ensure due process, but the University, UTFA and CAUT could have sought assurances from the Board on procedural fairness—had they done so, events might have proceeded differently. (See sections 5P and 5Q.)

Documents from late 1998 to early 2000, as well as testimony we had from representatives of UTFA, indicate that the various parties proceeded as

if Hospital and University matters could be severed. However, responsibilities for matters such as academic freedom and procedural fairness cannot easily be compartmentalized. It was not until after UTFA agreed to take over representation of Dr. Olivieri in both Hospital and University matters that the serious unfairness of the MAC proceeding was brought to light. (See sections 5P, 5Q and 5T.)

From late 1998 to the present, UTFA has devoted increasing resources to the cases of Dr. Olivieri and Drs. Chan, Dick, Durie and Gallie. Collectively, this has become the largest, most complex and most expensive academic freedom case in Canadian university history. In view of the direct public interest aspects of the case, it may also be one of the most significant ever, hence worthy of the time and other resources being invested.

After the January 1999 agreement failed to resolve important matters, CAUT decided to establish a Committee of Inquiry. Among measures taken to ensure independence from positions taken by CAUT, this Committee insisted that CAUT refrain from public statements and active involvement in the case until after publication of our report, and CAUT agreed and did so.

(3) Conclusions

1 | CAUT and UTFA failed to intervene at two critical junctures: in the late summer of 1998 they should have urged the importance of an inquiry structured so all parties would likely participate; and in early 1999 they should have urged the importance of due process in the MAC proceeding.

2 | Each of CAUT and UTFA subsequently invested substantial human and financial resources in what they consider to be a case exemplifying the principles of academic freedom, research and clinical ethics, and procedural fairness.

3 | CAUT and its member associations, including UTFA, should take steps to make university faculty members working in teaching hospitals aware of the importance of academic freedom, of the responsibility of all academics to uphold and defend it, and of the advice and assistance CAUT and member associations can provide to faculty members concerned about their academic freedom.

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5T | Public Interest, Public Policy, Contracts & Legal Representation

(1) Public interest & public policy

SAFETY OF PATIENTS lies at the heart of this controversy. It is in the public interest that physicians be obligated to inform their patients of possible harm from treatments, whether experimental or not, and that clinical researchers be free to communicate findings of unexpected risks to trial subjects and others with a right or need to know. Society endeavours to protect these public interests through a web of public and institutional policies which include legislation, ethical guidelines set by professional bodies and granting councils, and such generally acknowledged rights as academic freedom. The present case shows that existing policies are inadequate to protect these interests from improper pressures by industrial sponsors of research.

In the case under consideration, a drug manufacturer, Apotex, attempted on the basis of a contract to prevent a clinical professor of medicine, Dr. Olivieri, from fulfilling her obligations and exercising her rights. During the first two and one-half years of the controversy (1996–1998), Dr. Olivieri had legal support through the Canadian Medical Protective Association (CMPA), but the CMPA legal counsel was mandated in the first instance to minimize her legal exposure as an individual physician, not to serve broader institutional interests and objectives. It was the responsibility of the Hospital for Sick Children and the University of Toronto to protect the independence and academic freedom of researchers, as well as the authority of clinicians to act in the interests of trial subjects and patients.¹ Neither the Hospital nor the University acted effectively to protect these institutional interests and objectives, or to protect Dr. Olivieri's rights from infringement by Apotex (until January 1999). Defending the academic freedom of faculty members and promoting academic freedom as a vital principle are prominent among the objectives of CAUT and UTFA, yet neither took any effective action in this case until November 1998, three months after they were made aware of it. (See sections 5.G(4), 5.L, 5.N, 5.O.2(4)) and 5S.)

(2) Research contracts which offend public policy

Apotex's legal warnings were issued principally on the basis of the confidentiality clause in the contract for the randomized comparison trial (LA-01), which had a one-year post-termination communication ban. We requested a legal opinion from an authority on contracts, Daniel A. Soberman, Emeritus Professor and former Dean of Law, Queen's University. Professor Soberman addressed the obligations of a physician in both research trial and clinical settings in light of the case law, citing his own textbook on commercial law and another recent textbook on the law of contracts.² He wrote:

I believe it is clear from the above discussion that a physician is under a legal duty to disclose "material" or "significant" risks, and that failure to do so may well amount to the tort of negligence. The main issue of a physician's liability may be whether the risk has any reasonable basis. ... [I]f the researcher has a reasonable basis for her belief ... then failure to disclose is a breach of her legal duty to that patient and committing a tort.³

Professor Soberman examined the LA-01 trial contract in light of the jurisprudence and said:

To the extent that it prohibits a physician from disclosing to a patient information that the physician has acquired pursuant to her research (or otherwise), this clause is illegal and void if there is material or significant risk to the patient. The patient must be given the opportunity to decide whether to proceed or continue with the treatment. In these circumstances, the researcher does not have to establish the complete accuracy of her concern—a risk is a risk, not a certainty—but only that it was not an unreasonable concern.⁴ (emphasis in original)

The documentary record shows that Dr. Olivieri had a reasonable basis for her concerns. In both instances of identification of unexpected risks of the drug L1, the identification was based on detailed review and analysis of the relevant data in light of the current medical literature. In the first instance, loss of sustained efficacy of the drug identified in a trial setting, Dr. Olivieri's assessment was supported by Dr. Brittenham, himself a hematologist and an expert in disorders of iron metabolism, and she submitted a report to the Research Ethics Board (REB) based on the numbers of patients in well-defined categories of risk from iron overload. The Chair of the REB agreed that she had an obligation to disclose the risk to trial participants and directed her to do so. In the second instance, progression of liver fibrosis identified in a non-trial clinical setting, Dr. Olivieri made the identification of risk in conjunction with the assessments of two experts—the liver pathologist Dr. Cameron and Dr. Brittenham—and together they prepared a detailed scientific report on the identification. (See sections 5E and 5K.)

Thus, it appears unlikely that any court would have enforced the confidentiality clause in the LA-01 contract in the circumstances central to this case: disclosing identified risks to patients being treated with the drug L1.⁵

The LA-01 contract was in compliance with existing policy and practice on contract research at the University of Toronto and HSC (see sections 5A(3), 5N and 5O). Thus, the existing policy allowed the signing of contracts that offend public policy. Acknowledgment of this came on March 26, 2001 when the University announced that it and its affiliated teaching hospitals intended to change their policies so as to ensure that contracts for clinical research could not contain a clause prohibiting disclosure of findings of risk.⁶

(3) CMPA legal representation

Dr. Olivieri and Dr. Koren immediately notified the Hospital and the University in May 1996 that Apotex had terminated the trials and issued legal warnings to them.⁷ Dr. Olivieri also contacted Mr. Joseph Colangelo, of the law firm of McCarthy Tétrault which provides legal representation to CMPA members. Mr. Colangelo was joined by Mr. Steven Mason, and they and occasionally others from the same firm continued to be involved in the case until late 1998. It is not clear from the documentary record whether Dr. Olivieri expressly requested direct legal support, or back-up legal support from either the University or the Hospital in the early stages of the dispute with Apotex, and this issue itself became part of the controversy. It has been suggested that since Dr. Olivieri had access to legal counsel (CMPA), this was adequate and was all that was needed.⁸ Because of this, we review the CMPA coverage below. As our review shows, even if Dr. Olivieri did not specifically request legal assistance from the Hospital and the University, there were institutional interests and principles that required defending. The Hospital and the University should have ensured that they were legally represented in the dispute arising from Apotex's legal warnings to Dr. Olivieri, and that her academic freedom was vigorously protected, by directly engaging Apotex and its legal counsel at the institutional level.

It is clear from an extensive record of correspondence that Mr. Colangelo and Mr. Mason diligently and competently represented Dr. Olivieri as an individual facing potential law suits. The CMPA as an organization and Mr. Colangelo and Mr. Mason also went beyond this in important instances to protect Dr. Olivieri's academic freedom and the public interest. It is also clear that the CMPA devoted very substantial resources to this case, thus demonstrating the seriousness with which the CMPA and counsel from McCarthy Tétrault viewed the Apotex legal warnings. Nevertheless, the

CMPA legal coverage was, for various reasons, unable to provide all of the advice and perspective that Dr. Olivieri required.

The CMPA is “a medical mutual defence organization,” an organization of the profession whose slogan is “By physicians, for physicians.”⁹ Defence of academic freedom and defence of principles of clinical and research ethics are not its primary concerns. CMPA counsel were not representing the patients who had been enrolled in the terminated trials, the institutions, or any other third parties with a principled interest in the dispute. Having determined that Dr. Olivieri “had significant legal exposure,” her CMPA counsel advised what they termed a staged approach, designed to minimize this exposure.¹⁰ In practice this meant that lengthy deliberations between Dr. Olivieri and CMPA legal counsel preceded confirmation by CMPA of its support, and a procedure whereby Dr. Olivieri was advised to first inform Apotex and await its reply, before disclosing information about L1 to any third party. It also meant that CMPA did not advance one available defence against the legal warnings, and did not consistently advance a second available defence.

Irrelevance of the LA-01 contract to the risks identified in LA-03 data. Apotex based its legal threats primarily on the contract for the LA-01 trial, but the two findings of unexpected risk that Apotex wished to keep confidential were based on data from the patient cohort of a different trial—the long-term trial (LA-03). The contract for the LA-03 trial contained no confidentiality clause. No other contract could be read as applying to the LA-03 data, as the LA-03 contract was signed later than any of the other L1 contracts with Apotex and it expressly “supplanted” any previous contract that might have pertained to the LA-03 patient cohort.¹¹ Thus there was *no* contractual basis for Apotex’s warnings of legal action for breach of contract in relation to disclosure of the identified risks to patients, or anyone else. The CMPA lawyers never advanced this fact as a defence.

Confidentiality clauses offensive to public policy. As discussed above, for the purposes Apotex invoked it against Dr. Olivieri, the confidentiality clause in the LA-01 contract would likely be found by the courts to be legally void as against public policy. However, CMPA counsel initially did not advance this defence. As discussions between McCarthy Tétrault lawyers and CMPA staff continued during the summer of 1996, a senior lawyer in the firm noted that such a defence would be “more likely to succeed if the disclosure (of risk) is made to... the Health Protection Branch [of Health Canada],”¹² that is, if made under what could be viewed as a statutory requirement. In early August 1996 CMPA formally agreed on this basis to provide coverage to Dr. Olivieri in the

event Apotex took legal action in response to her informing the Branch of the first unexpected risk (loss of sustained efficacy).¹³

However, CMPA initially suggested it would not provide coverage if Dr. Olivieri disclosed the risk to the scientific community.¹⁴ It was only after she disclosed the risk to HPB on August 14, 1996, and HPB declined to assure her that it would communicate this finding to regulators in other countries where L1 was being used, that CMPA agreed to provide coverage for her intended presentation of the finding at the December meeting of the American Society of Hematology (ASH).¹⁵ Dr. Olivieri was assisted in persuading CMPA of the importance of communicating adverse findings on the drug at the forthcoming ASH meeting, by Sir David Weatherall (University of Oxford) and Dr. David Nathan (Harvard University), who spoke with Mr. Mason.¹⁶ By August 19 the CMPA and Dr. Olivieri's CMPA lawyers appear to have decided that, in this instance, the matter of contract clauses that offend public policy could be viewed as within their mandate, and advanced this defence. In a letter of that date to Apotex's legal counsel, Mr. Colangelo wrote:

Dr. Olivieri... will proceed to submit the abstracts [to ASH] for publication even if Apotex does not approve of the text of same. In our view there is an overriding *public interest* in the publication of the data and this must override any duty of confidentiality which Apotex claims Dr. Olivieri owes to it... If it is the intention of Apotex to commence legal proceedings to attempt to restrain Dr. Olivieri from taking this step, then I am instructed to accept service on her behalf...^{17*} (emphasis added)

Dr. Olivieri's identification in early February 1997, in data of the LA-03 trial, of the second and more serious unexpected risk of L1 was more likely to diminish the prospects for licencing the drug than the first risk she identified. Apotex expressed concerns to this effect and issued another legal warning.¹⁸ In response to this warning, CMPA counsel advised Dr. Olivieri to withdraw several abstracts she had already submitted to upcoming conferences in Europe and the United States, and she complied. Some weeks later, after learning that Apotex would be presenting its position that L1 was effective and safe at a conference, CMPA agreed to provide legal support to Dr. Olivieri's presentation of her finding at two conferences, in Malta in April 1997 and in Cambridge, Massachusetts in June 1997.

*Mr. Colangelo quite properly invoked this principle in regard to both of the two abstracts, one reporting LA-03 data in which the risk of loss of efficacy had been identified, and another reporting LA-01 data. It was important (though perhaps less urgent) to report LA-01 data, which was covered by the LA-01 confidentiality clause. One reason for its importance was that, although (on average) patients in the L1 arm of the randomized trial (LA-01) had been on L1 for a shorter period than patients in the long-term trial (LA-03), when the trials were terminated, fifteen LA-01 patients had been on L1 for the full two year period specified in the protocol, and data on their treatment also showed loss of efficacy, though less pronounced than in the long-term treatment (LA-03) cohort. (See section 5H(4).)

In summary, the public interest defence was advanced by CMPA counsel in regard to the abstracts for the 1996 ASH meeting and in regard to the abstracts presented in April and June 1997, but not in connection with the abstracts withdrawn in early 1997 on CMPA legal advice. (See section 5I(1) for citations of abstracts and correspondence.) Thus in regard to some of her intended publications, Dr. Olivieri's academic freedom was not protected.

In a discussion with Mr. Mason on December 16, 2000, this Committee raised questions about both of the possible lines of defence to the Apotex legal warnings. Mr. Mason did not have the benefit of reviewing files on the case at this time, and replied only in general terms. He said that lawyers at McCarthy Tétrault had assessed the situation and determined that "Dr. Olivieri had significant legal exposure." He noted two aspects of the situation: the documentary record reviewed by McCarthy Tétrault lawyers; and Apotex's record in using litigation.¹⁹ From our perspective, it remains unclear as to why CMPA counsel did not advance the line of defence that the LA-03 data was under no restriction, and unclear why they did not advance the "public interest" defence prior to August 1996, or consistently thereafter.

The staged approach. As recorded in documents of the time, and confirmed to us by Mr. Mason, throughout the period during which the legal warnings were issued, Dr. Olivieri's CMPA counsel advocated a staged approach.²⁰ As noted above, this approach was designed to minimize Dr. Olivieri's legal exposure as an individual and, as such, it was effective to the extent that Apotex did not actually launch any court action against her during the period when she had CMPA representation. However, because it resulted in delays in communication, and withdrawal of some abstracts already sent, it was not always effective in protecting her academic freedom. Thus, because the CMPA representation emphasized protecting her personal liability position, Apotex was able to infringe her rights by issuing legal warnings, without actually launching a court action and risking losing that action on the basis of one or both of the lines of defence that were available to Dr. Olivieri.

At the beginning of February 1997, the "staged approach" advised by the CMPA came into conflict with Dr. Olivieri's ethical obligations as a treating physician. During the preceding weeks, Drs. Olivieri, Brittenham, and Cameron carried out a retrospective review of LA-03 data to determine whether or not L1 posed a chronic risk of liver damage. She consulted CMPA on courses of action should a risk to patients be identified. Mr. Mason reported to us that CMPA again advised the staged approach.²¹ It was confirmed in early February that L1 was the probable cause of progression of liver fibrosis in some patients in the LA-03 cohort, and Dr. Olivieri then had

an obligation to inform patients. On this occasion, instead of first informing Apotex and then awaiting a response before taking further action, she informed patients on February 4, the same day she informed Apotex. On this occasion, Dr. Olivieri departed from the staged approach without informing her CMPA counsel, as counsel recorded on learning of her action three weeks later.²² Thus, she fulfilled her ethical obligation, but at the same time she potentially assumed the entire risk of Apotex legal retaliation herself. After they learned of this action, CMPA counsel continued to provide legal support, but appeared to urge greater caution through advising Dr. Olivieri to withdraw abstracts already submitted.

Joint CMPA legal representation of Dr. Olivieri and Dr. Koren. A potential limitation to the CMPA representation was the fact that the CMPA counsel decided that Dr. Olivieri and Dr. Koren should be represented jointly, because one of the first three legal warnings issued in May 1996 had been issued to both of them. That this might not have been in Dr. Olivieri's interest is more easily seen with the benefit of hindsight, because it took quite some time to become clear that Dr. Koren was in fact an advocate for the Apotex position that L1 presented no unexpected risks. (See sections 5H, 5L, 5N and 5R.) Once Dr. Koren's stance was understood, he could no longer be considered as being under legal threat from Apotex in regard to communicating about risks of L1, but rather as being in a position to communicate CMPA legal advice to Apotex, thus potentially compromising their representation of Dr. Olivieri. At this point (March 1997) Dr. Olivieri asked for separate representation.²³ CMPA agreed and discontinued representation of Dr. Koren in the matter of the Apotex legal warnings, as Mr. Mason confirmed to us.

(4) The positions of the Hospital & the University on the LA-01 contract

The Hospital appears to have conducted itself as if Apotex's attempts to impede Dr. Olivieri from implementing the directive by its Research Ethics Board and exercising her academic freedom were not its concern. Although she had informed the HSC administration on May 25, 1996 of Apotex's actions, and Dean Aberman apprised the Hospital of his meetings with Apotex and Dr. Olivieri in early June, we have no record of any direct HSC involvement in the matter until her CMPA counsel Mr. Mason requested a meeting with HSC Vice-President Dr. Alan Goldbloom and Dr. O'Brodovich in mid-July 1996 (see sections 5G(1) and 5G(4)). Various aspects of the dispute with Apotex were then discussed. With regard to Apotex's warnings

about enforcement of confidentiality about information on LI, Mr. Mason's notes of the meeting recorded:

The issue with respect to Dr. Olivieri's contractual obligations is a legal matter which the Hospital does not wish to involve itself in. The Hospital did indicate that they would speak to their counsel about this issue, Bill Carter of Borden & Elliot, and I agreed to speak with him.²⁴

Mr. Mason reported to us that he and his colleague Mr. Colangelo had a number of discussions with HSC counsel Mr. Carter on various issues during this period. He said that he at no time requested that the Hospital provide additional legal support to Dr. Olivieri, and gave as his reason his distinct impression that, from his initial contacts with Hospital representatives, they were displeased with Dr. Olivieri. He explained that he and Mr. Colangelo became concerned that her interests as an individual might be compromised should the Hospital become directly involved in her individual legal representation in the dispute with Apotex. Mr. Mason said that he attributed the apparent displeasure of HSC officials to three factors: (i) Dr. Olivieri's opposition to their plan to decentralize the sickle cell disease (SCD) program (see section 5.M); (ii) Dr. Koren had told senior HSC administrators privately that Dr. Olivieri had over-reacted to the data showing loss of efficacy of the drug,* and Apotex's Expert Advisory Panel had also said this; and (iii) Dr. Olivieri's dispute with Apotex might adversely affect relations between the Hospital and industrial sponsors of research.

According to the available documentary record, it was not until more than a year later, in September 1997, that the Hospital asked its legal counsel in the firm of Borden & Elliot for an opinion on the confidentiality clause in the LA-01 contract. This request came after a number of scientists inside and outside HSC had raised their concerns with HSC administrators and Dean Aberman that, in their perception, the Hospital and the University had not provided Dr. Olivieri with effective support. The memo from HSC legal counsel said:

Whether or not it was enforceable would depend on the specific facts (whether there were relevant *public policy concerns* about information relating to public health and welfare, whether *the agreement had been amended*, etc.) On its face, without reference to specifics, *it was probably enforceable.*²⁵ (emphasis added)

*In connection with this information of Mr. Mason, we note that on May 2, 1996, Dr. Spino of Apotex wrote to HSC REB Chair Dr. Zlotkin that, "This same view [on Dr. Olivieri's analysis of LA-03 data on loss of sustained efficacy] was expressed by Dr. Koren, a co-investigator in the LA-03 study, who stated in a meeting on February 29, 1996 ... that in his opinion, this information was the type that might be included in an annual report to the REB, rather than an urgent report noting 'unexpected' findings."

It was precisely “public policy concerns” that have been at issue in the entire controversy from the outset, yet the Borden & Elliot memo did not explore this consideration. Moreover, the relevant clause of the 1993 LA-01 contract was amended by the later LA-03 contract. Specifically, to the extent that the LA-01 confidentiality clause might have been considered applicable to any LA-03 data (as Apotex maintained from May 24, 1996 onward), it was no longer applicable after the LA-03 contract was executed in October 1995, because that contract expressly “supplant[ed] any other previous agreement” pertaining to the LA-03 trial, and that contract had no confidentiality clause. *It appears that Borden & Elliot was not given a copy of the LA-03 contract to review.*

As to Dr. Olivieri’s responsibilities, the Borden & Elliot opinion said:

I would prefer not to comment on *the physician’s disclosure responsibilities*, as Borden & Elliot was not advising Dr. Olivieri and she had already obtained legal advice through CMPA. ... *You confirmed that you would not require advice on this point at this time.*²⁶ (emphasis added)

It is relevant to note that the Borden & Elliot memo went on to offer a view on the matter of confidentiality clauses at the level of policy:

We discussed this point and determined that *the Hospital could agree to delay disclosure* of research results at the sponsor’s reasonable request (for example, *to give the sponsor time to file patent application or do some damage control*).²⁷ (emphasis added)

No legal opinion on the confidentiality clause in the LA-01 contract obtained by the University, if any, was available to us. However, in its public statement on the case of December 3, 1998, the University said:

The contract entered by Dr. Olivieri with Apotex violated University policy and would not be administered by the University. We agree with Dr. Olivieri that she made a mistake in signing the contract which included offensive publication restrictions, and we would not, and did not, either support this contract or the enforcement of these offensive provisions.²⁸

In fact, the LA-01 contract did *not* violate the University’s publication policy, as noted earlier.

The agreement signed on January 25, 1999 by the Hospital, the University, and Dr. Olivieri contained a provision for back-up legal support for Dr. Olivieri, at Clause 8:

If Dr. Olivieri is required to defend herself in any legal action brought by Apotex arising out of facts which occurred prior to January 25, 1999 for which CMPA refuses to provide coverage, HSC will pay her costs of defending such an action. In the unlikely event that Apotex were successful, HSC agrees to indemnify Dr. Olivieri with respect to any award or judgment.²⁹

The circumstances which led to this agreement are outlined in sections 5M and 5N above.

(5) Subsequent legal representation for Dr. Olivieri

The CMPA provided additional advice to Dr. Olivieri on her Hospital employment and working conditions, and on the Naimark Review. As matters progressed in the autumn of 1998, and she and her principal supporters became increasingly concerned about actions by HSC administrators, she obtained legal representation on HSC matters from two other lawyers, Mr. Clayton Ruby and Ms. Beth Symes. They represented her on Hospital and University issues until early 2000. Their fees were not covered by the CMPA. These issues included: the Hospital's removal of Dr. Olivieri from her HSC program directorship; the negotiations leading to the agreement of January 25, 1999; the mediation process that attempted to implement outstanding terms of that agreement and resolve some other issues; the reduction of medical staff resources for the hemoglobinopathy clinic; and the misconduct complaint against Dr. Koren. Ms. Symes also represented Dr. Olivieri in the Medical Advisory Committee (MAC) proceedings, from December 1998 until early 2000. (See sections 5M, 5N, 5P and 5R.)

The need to engage private legal counsel resulted in significant measure from the Hospital's lack of an adequate grievance procedure. In complex issues, when no such procedures exist, individuals can face financially ruinous legal expenses. An indication of the scale of expense can be seen from clause 9 of the January 25, 1999 agreement: "HSC will indemnify Dr. Olivieri for actual legal and other expenses incurred to date to a maximum of \$150,000." The Hospital paid the full amount.³⁰ Dr. Olivieri reported to this Inquiry that she incurred very large additional expenses subsequent to that agreement for legal representation in matters not resolved by that agreement.

The University of Toronto Faculty Association (UTFA) had been providing assistance to Dr. Olivieri from late November 1998 on matters related to her position as a clinical professor in the Faculty of Medicine, such as her right to academic freedom and her right to due process in both University and Hospital matters (see sections 5M and 5N). Around the end of January 2000, after the HSC Medical Advisory Committee issued a report adverse to Dr. Olivieri that was based on allegations not disclosed to her, UTFA agreed to assume responsibility for more aspects of this very complex case (see section 5P and 5Q). As a result, legal advice was henceforth provided to Dr. Olivieri both by UTFA staff counsel Ms. Allison Hudgins, and by lawyers from the firm of Sack, Goldblatt and Mitchell which regularly provided UTFA with legal counsel.

In addition to lifting some of the financial burden from Drs. Olivieri, Chan, Dick, Durie and Gallie (the latter four by this time were substantially engaged

in aspects of the dispute), the change in representation had two other important results. First, Ms. Cathy Lace and other lawyers from Sack, Goldblatt and Mitchell succeeded in obtaining from the MAC the substance of the allegations and some of the related testimony put forward a year earlier to the MAC by Dr. Koren, Dr. O’Brodivich and others. None of this had previously been disclosed to Dr. Olivieri. Second, Ms. Hudgins and Ms. Lace, in the course of a review of the available documents, evaluated the LA-03 contract and recognized its double significance: (i) that no contractual grounds existed to restrict disclosure of the two risks identified in LA-03 data; and (ii) that Apotex had the clear contractual right to terminate the LA-03 trial, not merely its sponsorship of that trial.

The importance of Clause 8 in the agreement of January 25, 1999 was emphasized in January 2001, when the Hospital for Sick Children agreed to indemnify Dr. Olivieri for certain expenses in a current legal proceeding between Apotex and her. On December 19, 1999, the CBS television program *60 Minutes* broadcast statements by Apotex officials (notably its President and CEO, Dr. Barry Sherman) which Dr. Olivieri considered materially injurious to her professional and personal reputations. In early 2000, she brought an action for damages against Dr. Sherman and Apotex. They responded with a defence and a counterclaim: that Dr. Olivieri had damaged the reputation of their product L1, and their corporate reputation, in statements made in various public contexts.³¹ (See section 5I.) When the CMPA refused legal support for any part of this action, Dr. Olivieri requested support from the Hospital, pursuant to the January 1999 agreement. On January 8, 2001, HSC President and CEO Mr. Michael Strofolino advised her counsel that, “as an interim measure, HSC is willing to indemnify Dr. Olivieri for reasonable legal expenses that are incurred in respect of the [Apotex] counterclaims alone.”³² Under this arrangement, Dr. Olivieri is free to choose her own independent legal counsel.

(6) Conclusions

1 | CMPA legal representation of Dr. Olivieri was effective in important aspects of this complex dispute. The documentary record available to us shows that no other organization or institution provided effective support to her during the first two and one-half years (late May 1996 to late November 1998). It was the assurance of CMPA backing that enabled to her inform the regulatory authorities of the risks she identified, and to submit abstracts to conferences on these findings. In these matters it was CMPA legal representation that protected both Dr. Olivieri’s academic freedom and the public interest. In so doing, CMPA took risks of incurring substantial additional expenses by interpreting its mandate as encompassing the public interest.

2 | CMPA representation was not always sufficient. On several occasions in early 1997, in the face of continuing legal warnings by Apotex, CMPA advised Dr. Olivieri to withdraw conference abstracts on the risk of progression of liver fibrosis that she had already submitted, and she did so, even though this risk was identified in LA-03 data that was not subject to any confidentiality restriction. In these instances, her academic freedom and the public interest were not protected. On one important occasion, Dr. Olivieri did not follow the staged approach advised by CMPA. This was on February 4, 1997, when she advised patients of the risk of progression of liver fibrosis immediately after it was identified, so as to fulfil her ethical and legal obligation, on the same day that she also informed Apotex.

3 | The Hospital for Sick Children and the University of Toronto as institutions had interests and responsibilities regarding clinical and research ethics, and academic freedom. The institutions should have acted effectively to protect these principles. Neither took effective action until January 25, 1999, more than two and a half years after the first legal warnings were issued and then only after the intervention of outside parties.

4 | It was not until 2000, when UTFA and the firm of Sack, Goldblatt and Mitchell became more extensively involved, that important information came to light in regard to the contracts: that LA-03 data was not subject to any confidentiality restriction; and that the LA-03 contract gave Apotex the right to terminate that trial. Lawyers from Sack, Goldblatt and Mitchell succeeded in obtaining disclosure of the allegations and testimony against Dr. Olivieri in the MAC proceedings, as a result of which the serious unfairness of those proceedings became clear.

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5U | The Involvement of Government Regulatory Agencies

(1) Introduction

THE REGULATORY AGENCIES IN CANADA and the United States were consulted by Dr. Olivieri regarding L1 trials from the beginning. More recently there have been licencing applications for L1 by Apotex in several jurisdictions, including Canada and the European Communities. We review these matters only to the extent necessary to understand topics related to our mandate. It was the original hope of both Dr. Olivieri and Apotex that L1 would prove sufficiently safe and effective that it could be licenced for therapeutic use. Even when Apotex terminated the Toronto trials in May 1996, they both still hoped it could be licenced. At that point, Dr. Olivieri wanted the trials to be continued so fully informed patients still benefiting from the drug could continue treatment, and causes of the unexpected risk of loss of sustained efficacy in some patients could be elucidated. However, Apotex was opposed to informing patients, the regulators or anyone of the risk Dr. Olivieri had identified and it refused to reinstate the trials.

The responses of regulators to Dr. Olivieri's findings on risks of L1, Apotex's termination of the Toronto trials and legal warnings to Dr. Olivieri, and Apotex's allegations to regulators against Dr. Olivieri and her work, are matters of public interest and central to the controversy. Apotex's licencing applications and Dr. Olivieri's opposition to them (after she learned of the basis for them) are relevant to our Inquiry for the additional reason that these became associated with anonymous letters against Dr. Olivieri and her supporters, another central element in the widening controversy from late 1998 onward.

(2) Government regulatory agencies

Citizens of developed countries rely on government agencies to ensure that new drugs are properly tested for safety and efficacy before they are licenced for marketing. These agencies also are relied on to ensure that adverse effects which may occur after licencing are monitored. The influence of these regulatory bodies extends beyond their own countries, since governments of less developed countries may rely on decisions made elsewhere. The agencies in Canada, the USA and the European Communities are called the Health Protection Branch (HPB), the Food and Drug Administration (FDA), and the European Agency for the Evaluation of Medicinal Products (EMA), respectively. As a result of intergovernmental discussions, there is some similarity among their regulations, procedures and standards. In addition to formal regulatory activities, the staff of these agencies provide informal advice

to manufacturers and to clinical investigators engaged in the development of new drugs.

Legislation places great responsibility on manufacturers to ensure the accuracy and completeness of data collected in drug trials. The public expects governmental agencies to have the capacity and to be diligent in ensuring compliance with this responsibility. The Canadian *Food and Drugs Act* and *Regulations* contain strict provisions for data from clinical trials of a new drug submitted by the manufacturer in a licencing application. In particular, the *Act* and *Regulations* require that the manufacturer have, “(a) kept accurate records... of the results of clinical testing...; and (b) immediately reported to the Director all information he [the manufacturer] has obtained with respect to serious adverse reactions.” The manufacturer is required to “certify that all information and material included in the submission... are accurate and complete....” In regard to such certificates submitted by the manufacturer, “No person shall sign a submission certificate if... [any part of it]... , (a) is false or misleading; or (b) contains omissions that may affect its accuracy and completeness.”¹

Dr. Olivieri consulted with the HPB and the FDA on the conduct of trials and on the development of L1, on several occasions from the late 1980s onward. In the early 1990s the FDA advised her and American investigators that three trials should be performed for licencing purposes: a continuation of her pilot study as a long-term trial; a new randomized comparison trial; and a short-term safety trial to assess known acute-toxicity effects. The FDA also advised the investigators that a pharmaceutical manufacturer should be involved. Apotex agreed to acquire commercial rights for L1 and sponsor the three trials. These three investigational new drug trials were arranged under the guidelines of the relevant regulatory agencies in the countries where sites were organized. (See sections 5A to 5D.)

(3) Responses of the Health Protection Branch to events

There are questions as to whether the Canadian regulators applied the degree of oversight warranted by events in the L1 matter. In 1996, Dr. Olivieri identified an unexpected risk of L1, loss of sustained efficacy. When she moved to comply with a directive by the Research Ethics Board of the Hospital for Sick Children to inform patients and the regulators of this risk, Apotex abruptly terminated the randomized trial (LA-01) and the long-term trial (LA-03), and advised HPB of the terminations. The company issued legal warnings to deter Dr. Olivieri from advising anyone of this risk, but in defiance of the legal warnings and with CMPA legal support, she informed patients, and also met with HPB (in August 1996) to report on her findings and the actions of Apotex. (See sections 5F to 5I.) The following facts

should have resulted in HPB taking more significant action in 1996 than simply granting Dr. Olivieri an audience:

1. The two Toronto trials, including the randomized LA-01 trial, were prematurely terminated by Apotex for the reason that it did not wish patients in the trials to be informed of a risk of the drug;
2. Performance of the two Toronto trials was considered important for licencing by the FDA;
3. Apotex was using legal warnings to Dr. Olivieri to deter her from discharging duties imposed on her by the Hospital's REB;² and
4. Apotex's own Expert Advisory Panel (EAP) urged that both the LA-01 and LA-03 trials be reinstated.*

The HPB could have advised Apotex that a licencing submission would not be successful unless it could provide evidence on efficacy and safety comparable to that which the terminated trials were intended to provide. The company could have done this either by reinstating the Toronto trials, or by organizing new trials of comparable scope. The HPB could have asked for an independent review of the circumstances of the termination of the trials and the legal warnings. We have no evidence that HPB took such measures, despite the fact that later internal HPB memos show that its staff understood that further study of the drug was warranted.

Dr. Olivieri's report that the HPB declined to assure her that it would inform the regulatory agencies in other countries where L1 was in use, of the risk she identified, is of concern. It was following this refusal by HPB that CMPA agreed to provide legal support to Dr. Olivieri to publish her findings in the scientific community, so that investigators and physicians administering L1 in other centres would be informed. (See sections 5H and 5T.)

HPB staff became aware of some later events through a news article in the January 21, 1997 issue of *The Medical Post* outlining the dispute between Apotex and Dr. Olivieri, and summarizing events at the December 1996 ASH meeting. An internal HPB memo from early 1997 refers to this article, which also reported that the group of Drs. Victor Hoffbrand and Beatrice Wonke reported a finding of loss of efficacy from their long-term L1 trial in England

*The Report of the Apotex EAP, dated July 12-13, 1996, stated, "The Committee [EAP] strongly advises that all possible efforts be made to re-instate the studies in Toronto that have been discontinued so as to finish the studies and provide information that will be valuable to patients throughout the world. It would be particularly disadvantageous to the patients who have agreed voluntarily to participate in the current two studies [LA-01 and LA-03] not to have the ultimate benefit of their participation."

very similar to Dr. Olivieri's finding in the LA-03 trial. The memo appears to have been written prior to HPB staff learning from Dr. Olivieri that a second risk, progression of liver fibrosis, had been identified in early February 1997. The memo notes that the news article reported that Dr. Olivieri was of the view that further study of the drug's safety and effectiveness would be required, before it could be licenced for therapeutic use. The HPB memo concluded that "further investigation of L1 seems to be desirable."³

In early June 1997, three months after Dr. Olivieri had reported to the regulatory agencies on the second and more serious unexpected risk (progression of liver fibrosis), Dr. Agnes Klein, a Unit Head in HPB, wrote to two other HPB officials to say that there were "deficiencies in Dr. Olivieri's presentation." However, Dr. Klein's account of "deficiencies" actually served to show why the Toronto trials should have been continued beyond their termination by Apotex. She wrote that the "deficiencies" were:

1—There are no patients [in the LA-03 trial] on desferoxamine for comparison. Hence, we do not know what the rate of hepatic fibrosis progression would be for patients treated in this manner.

2—It is my understanding that once fibrosis sets in, it either arrests when the cause is removed, or sometime [sic], continues to progress, regardless of therapy, and regardless of whether the cause for it is removed. Such is the case in many instances of hepatic cirrhosis.

3—There is no discussion of the expected rate of progression for hepatic fibrosis in untreated thalassemic patients. At the very least some comparison with historical data should be made.⁴

In regard to Dr. Klein's first point, as HPB had been informed, there were patients on deferoxamine in the randomized trial (LA-01). HPB also had been informed that the LA-01 and LA-03 trials had both been terminated prematurely by Apotex. This "deficiency" might have been remedied by a continuation of the LA-01 trial, which was the *only* trial anywhere in the world designed to compare L1 with deferoxamine. As to her second point, Dr. Klein apparently did not appreciate that it had been established in the medical literature for more than a decade that deferoxamine therapy can arrest iron-induced progression of liver fibrosis.⁵ As to Dr. Klein's third point, Dr. Olivieri had provided relevant historical data in her report (sent to HPB on February 24, 1997), which summarized the data on the new risk, and gave references to the literature on both L1 and deferoxamine.⁶ It would not be ethically possible to mount a trial to answer the question raised in Dr. Klein's third point, as thalassemia major is a fatal disease if untreated (see section 2C).

We conclude from Dr. Klein's remarks that:

- In cases of serious dispute between a corporate sponsor and an investigator such as this, HPB should inform the investigator of the

allegations by the sponsor, should investigate the matter, and should then act to protect the public interest;

- HPB should recognize when it needs outside expert advice, and should get this advice, to protect the public interest.

Apotex applied to HPB for a licence to market L1 in Canada in early 1998,⁷ about a year after Dr. Olivieri had advised HPB of her finding that L1 caused progression of liver fibrosis in some patients.⁸ In April 1998, Dr. Klein referred a question to another official, “Is the data provided by the investigator, Dr. Olivieri adequate to support a claim of hepatotoxicity in humans?”⁹ The question suggests that Dr. Klein, an administrative officer of HPB, had reversed the onus of responsibility: instead of asking whether the manufacturer (Apotex) had provided sufficient data to establish an acceptable degree of safety, she asked whether harm had been proven by the investigator. She herself had written comments the year before (quoted above), the implication of which was that the premature termination of the Toronto trials by the manufacturer made it impossible to provide sufficient data on safety. Two HPB staff scientists replied to Dr. Klein’s question in September 1998, by which time Dr. Olivieri’s article on this risk appeared in *The New England Journal of Medicine* (1998).¹⁰ The staff scientists said that the article was inconclusive on progression of liver fibrosis and that Dr. Olivieri’s data were “insufficient and of questionable validity for regulatory purposes.”¹¹ They recommended that Dr. Olivieri “provide additional information.” Dr. Olivieri reported to us that HPB did not approach her with such a request. Rather, it was she who contacted HPB and asked for a meeting, after she obtained information from other sources about Apotex’s licencing applications. Once again, HPB staff appear to have reversed the onus and, having done so, they then did not approach the investigator to discuss the information they said was needed.

HPB knew that the Toronto trials had been prematurely terminated and not reinstated. It knew that Dr. Olivieri had identified a second and more serious risk, progression of liver fibrosis. HPB also knew that Apotex had been using legal warnings in efforts to deter Dr. Olivieri from complying with her obligations to report the risks. In internal memos, HPB staff in effect acknowledged that the premature termination of the trials resulted in there being inadequate study of the safety and efficacy of L1. Nevertheless, after Apotex submitted its licencing application, HPB did not approach Dr. Olivieri to ascertain her views (as principal investigator for the LA-01 and LA-03 trials) on the licencing application, and on the accuracy of Apotex’s supporting data, including the allegations against the quality of her work. HPB staff correspondence suggests that at times the onus of responsibility was reversed in the matter of establishing that L1 was sufficiently safe and

effective to be licenced as therapy. However, it is of note that at the time this report was completed, L1 had not to our knowledge been licenced in Canada.

In summary, the Health Protection Branch of Health Canada could have acted more robustly to protect the public's safety in a manner that Canadian citizens have a right to expect, in regard both to the L1 trials and to the subsequent licencing application by Apotex. If HPB felt constrained by existing policies or regulations, any such policies or regulations should be changed.

(4) Apotex's licencing applications

In the fall of 1997 Apotex made a Priority Review Submission to HPB for L1 under the name Deferrum.¹² This was followed in early 1998 by licencing submissions to regulatory agencies in several jurisdictions for L1 under the names Exferrum and Ferriprox, including a submission to HPB in which L1 was referred to by the name Exferrum.¹³ The company now stated that the short-term acute-toxicity trial at international sites (LA-02) was the "pivotal" efficacy and safety trial, and that the Toronto-based trials (LA-01 and LA-03) were "supportive studies."¹⁴ The company now stated that the data from the latter two were limited in quality because "the principal investigator [Dr. Olivieri] failed to adhere to the protocol."¹⁵ Apotex now alleged to regulators that "these [protocol] violations" constituted "the primary reason" it terminated the Toronto trials.¹⁶ In section 5F of this report we discussed the reasons Apotex gave as to why it terminated the trials, and the fact that "the reasons" changed as time went on. On the weight of the evidence in Apotex's own written statements in 1996 and 1997, we concluded that "protocol violations" were not the reason why Apotex terminated the Toronto trials in May 1996.

Dr. Olivieri reported to us that she was not informed by Apotex or by any regulatory agency that the company had made allegations against the quality her work in its submissions, nor was she informed of any other aspect of the company's L1 submissions. She said she first learned of these matters in July 1998 when she spoke at a conference in Australia on her finding that L1 posed a risk of progression of liver fibrosis. Following her talk, a member of the audience approached her and expressed surprise about this finding. This person then provided her with a copy of an Apotex Research document pertaining to its licencing submission to the Australian regulators.¹⁷ This document omitted mention of Dr. Olivieri's finding of this risk.*¹⁸

*Dr. Olivieri's report on the risk of progression of liver fibrosis was sent (in February 1997) to the regulatory agencies in the USA, Canada and Italy, with whom she had previous contacts in regard to the LA-01, -02, and -03 trials, and to the regulatory agency in India where L1 had been licenced since 1995. It was not sent to the regulatory agency in Australia or other countries, because she had not been apprised of any licencing activities by Apotex in these countries.

Apotex's claim to regulators that LA-02 was the pivotal trial for licencing and its attempts to discredit Dr. Olivieri and her work in regulatory submissions became central elements of the continuing L1 controversy. Apotex's allegations to regulators against Dr. Olivieri also became linked to events at the Hospital for Sick Children after the company made related allegations to members of the Hospital Executive in 1998. In this subsection we outline matters relevant to topics discussed in sections 5N, 5O, 5P, 5Q and 5R.

I. DR. OLIVIERI'S 1997 ASH ABSTRACT

In August 1997 Dr. Olivieri and Dr. Brittenham submitted an abstract for the December 1997 meeting of the American Society of Hematology (ASH). It was based on data obtained from review of the charts of some of the patients who had been enrolled in the randomized trial LA-01, and reported on the comparative efficacy of L1 and deferoxamine (DFO). The abstract noted that this trial had been "prematurely terminated in Toronto by Apotex Inc," but that some patients who had been enrolled in the L1 arm of that trial had continued on the drug for an additional period and had been monitored (see sections 5G(1) and 5H(1)). The abstract concluded:

[M]ean body iron burden increases over two years of L1 therapy despite excellent patient compliance; tissue iron reaches concentrations associated with iron-induced complications in 95% [of] patients, even those who begin therapy with relatively low initial body iron burdens. By contrast, less regular compliance with low doses of DFO appears to maintain mean body iron within optimal range.¹⁹

Thus, the abstract further confirmed the trend that had been observed in data of the long-term (LA-03) trial—that over time L1 lost sustained efficacy in a high proportion of patients. In addition it reported that L1 was significantly less effective than the standard drug DFO, hence also significantly less safe.

The 1997 ASH abstract played a well-documented role in the developing controversy. First, Apotex disagreed with its contents and its publication (see below). Second, Apotex subsequently (May 1998) alleged to HSC that this publication was evidence that Dr. Olivieri had been conducting unauthorized research. The allegation was incorrect—publication of the results of chart review did not constitute unauthorized research (see section 5P(9)). However, the allegation served Apotex's interests—as discussed here and in section 5Q, discrediting Dr. Olivieri was an aspect of Apotex's licencing efforts for L1. Third, Apotex's efforts through correspondence with Dr. Koren and Dr. O'Brodovich to obtain data reported in the 1997 ASH abstract, as well as to discredit Dr. Olivieri, resulted in some of the most important letters in the voluminous record of the L1 controversy. These included: several 1997 letters by Dr. Koren which contradicted some of his

testimony to the Naimark Review and the Medical Advisory Committee (MAC) inquiry (see sections 5O2, 5P, 5Q and 5R); Dr. Spino's May 22, 1998 letter to Dr. O'Brodovich alleging Dr. Olivieri had conducted unauthorized research (see section 5Q); and Dr. Moore's June 3, 1998 letter to Dr. O'Brodovich incorrectly stating that a research trial of L1 continued after May 1996 (see sections 5K and 5P).

Fourth, Drs. Koren and O'Brodovich cooperated in putting the 1997 ASH abstract forward as purported evidence of misconduct by Dr. Olivieri, both to the Naimark Review and the MAC inquiry. Fifth, legal counsel for the MAC said that the MAC regarded the abstract as evidence suggesting that the LA-01 and LA-03 trials continued after May 1996, so that, purportedly, patients who continued on L1 under the non-trial EDR arrangement were still subjects of research. Lastly, on the basis of testimony such as this, the MAC and the HSC Board of Trustees referred allegations of misconduct against Dr. Olivieri to outside bodies. (See section 5P for details and citations.)

Dr. Olivieri had sent a copy of a similarly worded draft of this abstract to Apotex "as a courtesy."²⁰ Dr. Spino responded on August 27, 1997 requesting data, as well as objecting the abstract:

[W]e are concerned about your overzealous approach to submitting abstracts for publication before there has been adequate review of the data. It appears that your goal is to actively and assiduously avoid a balanced, temperate and scientifically sound analysis of the data.²¹

Despite the Apotex objections,* Dr. Olivieri submitted the abstract to ASH. Approximately one month later, Apotex made a Priority Review Submission on L1 to HPB, disputing Dr. Olivieri's adverse findings on the drug, and also making an unspecified allegation against her:

The [LA-01] study was discontinued at the main site [Toronto] prior to the planned completion date due to problems with the principal investigator [Dr. Olivieri].²²

II. ALLEGATIONS OF "PROTOCOL VIOLATIONS"

The earliest record we have of an allegation by Apotex that Dr. Olivieri had committed or allowed significant protocol violations appears in the letter from Dr. Spino to her dated August 27, 1997 pertaining to her 1997 ASH abstract (cited above), more than a year after the Toronto trials were terminated. This letter contained several allegations, for instance, that Dr. Olivieri had

*Unlike the clear legal warnings to Dr. Olivieri against disclosure of adverse findings on L1 issued in the period May 1996—May 1997, other than in its ambiguous reference to "contractual obligations," Dr. Spino's August 27, 1997 letter does not appear to warn directly of legal consequences. Possibly this was because the one-year post-termination publication ban in the LA-01 contract had by then expired.

disregarded her “contractual obligations” to Apotex, and that her findings of the two unexpected risks of L1 were “unfounded.” The letter continued: “repeated protocol violations... seriously jeopardized the value of the data generated from your studies.”²³ However, Dr. Spino did not specify the alleged protocol violations, and this letter did not appear to give any more weight to the allegation regarding protocol violations than to other allegations in it. Indeed in the same letter Dr. Spino also wrote:

As you know very well, the trial was discontinued because of unilateral and precipitous actions taken by you without regard for the views and opinions of Apotex personnel or other experts and investigators in our trials.²⁴

It is clear from correspondence during February—May 1996 that Apotex regarded Dr. Olivieri’s report to the REB on the first unexpected risk of L1, and her consequent revision of the patient information and consent forms, as “unilateral and precipitous actions.” Dr. Spino thereby appears to have confirmed in August 1997 what he had written in June 1996—namely, that Apotex terminated the Toronto trials because Dr. Olivieri had moved to inform patients of a risk and the company wished to prevent her from doing so. (See sections 5E and 5F).

Minor protocol violations are not uncommon in clinical trials. They can arise for such reasons as personal circumstances of a trial participant making it necessary to reschedule the date of a monitoring test. The issues of whether there were significant protocol violations and, if so, whether they materially affected the data from the Toronto trials, are now before a court of the European Communities, as noted below.

Self-contradictory aspects to Apotex’s allegations of significant protocol violations were noted in section 5F. For instance, the company itself published findings based on data from the same LA-01 and LA-03 trials, and then used these publications in 1997 correspondence with regulators, yet apparently made no mention of protocol violations (see sections 5N(5) and 5P(14)).

III. APOTEX’S DISAGREEMENT WITH DR. BRITTENHAM

As noted in section 5U(2), the Canadian *Food and Drugs Act* and *Regulations* require the manufacturer to certify the accuracy of data included in a regulatory submission. The data for the primary efficacy endpoint in both the Toronto trials was hepatic iron concentration (HIC). Approved protocol amendments for the LA-01 trial specified that, “to ensure uniformity of assessment,” assay of HIC would be conducted in Dr. Brittenham’s laboratory.²⁵ He also made HIC determinations for the LA-03 trial. Although this important role was assigned to Dr. Brittenham, Apotex omitted to sign a relevant contract with him. The contract for LA-01 provided funding for

patients' airfare between Toronto and Cleveland, but did not provide funds for the actual testing in his laboratory.²⁶ There is no reference to Dr. Brittenham in either the LA-01 or LA-03 contract, each of which was signed by three persons: Dr. Koren, Dr. Olivieri and a representative of Apotex.

Shortly after it terminated the Toronto trials and issued legal warnings to Dr. Olivieri on the basis of the confidentiality clause in the LA-01 contract, Apotex wrote to Dr. Brittenham to ask if he would continue his "relationship with Apotex in the development of deferiprone."²⁷ The letter said that a "confidentiality" agreement would be required of Dr. Brittenham in any such relationship. Later in 1996, the company requested audited source data from Dr. Brittenham for the primary endpoints for LA-01 and LA-03, the HICs for trial participants.²⁸ Dr. Brittenham reported to us that the advice of his legal counsel, when this request came in the second half of 1996, was that he was not obligated to provide this data, but if he wished he could choose to do so on his own terms. Dr. Brittenham agreed to provide it on certain conditions. As reported by Dr. Spino, these were, "that we [Apotex] could conduct an audit [of source data generated by Dr. Brittenham] only if Apotex paid for all the SQUIDs and biopsies already completed over the past 6 years and, in addition, paid him [Dr. Brittenham] to be present for the entire audit."²⁹ Apotex refused his terms and he did not provide the source data.

There are several aspects of this that are of interest. First, despite the importance of this data to Apotex for its intended licencing applications, it did not initiate legal action in an effort to get the data under the one contract it had with Dr. Brittenham: a contract for consulting work on the short-term toxicity (LA-02) trial.³⁰ Second, Dr. Brittenham's employer, Case Western Reserve University, provided him with legal counsel. (Neither the University of Toronto nor the Hospital for Sick Children provided legal support to Dr. Olivieri in her dispute with Apotex until the agreement of January 25, 1999.) Third, in a submission to regulators in September 1997, Apotex made allegations against Dr. Brittenham's HIC data: "any analysis based on pooled data [from biopsy and SQUID] is flawed and inaccurate."³¹ This Apotex criticism of the quality of Dr. Brittenham's work is curious, because the protocols for the Toronto trials, to which Apotex had agreed, indicated that biopsy and SQUID data could be pooled in this way, due to the long-established, very high correlation between them. It is also of note that Apotex Vice-President Dr. Spino signed the 1995 LA-01 protocol

*This point is of interest because, in one of its legal warnings to Dr. Olivieri (dated May 26, 1997), Apotex's counsel suggested that the three-year publication ban in her LA-02 contract, a consulting contract similar to Dr. Brittenham's LA-02 contract, applied to data from the Toronto trials. Dr. Olivieri's counsel rejected this argument and it was not subsequently pursued by Apotex's counsel.

modification assigning to Dr. Brittenham responsibility for determining HICs for trial subjects from pooled data.³²

Lastly, in the extensive documentary record available to us, the particular allegation by Apotex that Dr. Olivieri committed such significant protocol violations in the Toronto trials that the data were materially compromised was made subsequent to two events:

- the disagreement in 1996 between Apotex and Dr. Brittenham over access to data;
- publication of the 1997 ASH abstract by Drs. Olivieri and Brittenham reporting a finding that L1 was significantly less effective than DFO.

It appears that this allegation by Apotex was accepted by the European regulators (EMA) in regard to the randomized comparison trial LA-01, and was a factor in their granting of a restricted licence to the company for L1 (see the European Public Assessment Report on L1 dated August 25, 1999, Scientific Discussion section, pages 7, 10, and 11.) Events pertaining to this license are outlined below.

IV. APOTEX'S CLAIM THAT LA-02 WAS THE "PIVOTAL" EFFICACY & SAFETY TRIAL

The LA-02 trial was designed to satisfy a specific, limited requirement that the FDA imposed because L1 was known to have acute toxicity effects³³ in a small minority of patients. The planned short (one-year) duration for it was adequate for this specific purpose. The trial was designed for Apotex by Drs. Olivieri and Brittenham in 1994, and its limited purpose was outlined by them in a journal article published in April 1995.³⁴ Dr. Spino himself, in a letter to Dr. Olivieri dated February 14, 1996, stated, "the LA-02 trial... is a safety study of shorter duration (1 year)."³⁵

The context in which Dr. Spino made this statement is relevant. It suggests that, at the time, he accepted that LA-02 could not be regarded as a pivotal efficacy and safety trial for licencing purposes. In this letter, he was responding to the draft report Dr. Olivieri intended to submit to the REB of the risk of loss of efficacy of L1. In that report, she wrote that her identification of risk in LA-03 data "may be relevant" to the LA-01 and LA-02 trials.³⁶ In his reply letter of February 14, 1996, Dr. Spino proposed that her reference to LA-02 be "excluded," for the reason that it was "a safety study of shorter duration."³⁷ In other words, he was suggesting that the loss of sustained efficacy identified in data of patients in a long-term trial was not relevant to patients in a trial (LA-02) of planned one-year duration. He did

not suggest that it was irrelevant for patients in the LA-01 trial, whose planned duration was two years, plus one year of follow-up.

The LA-02 trial protocol specified that its “primary objective” was to determine the incidence of known acute toxicity effects of L1. Determination of the efficacy of the drug was its “secondary objective.” Because the trial was designed as short-term (one year) and efficacy was a secondary objective, the convenient but less accurate measure of efficacy of iron-chelation treatment, serum ferritin concentration, was specified for it. (See section 5B(2).) In contrast, the protocols for the longer-term Toronto trials (LA-01 and LA-03) both specified the only accurate measure of efficacy, hepatic iron concentration (HIC,) be determined at baseline, annually, and on termination, for all trial participants. Therefore, the LA-02 trial, by design, could not establish whether L1 was an effective iron-chelator in the long term. It probably could not accomplish this even if it was extended in time (as it was, in effect, under a very similar LA-06 protocol),³⁸ because it did not use HIC for all participants. Data from this trial could not be used to establish comparative efficacy of L1 with the standard iron-chelation drug, deferoxamine (DFO), not only because it was not a randomized comparison trial, but also because the efficacy of DFO had been established in trials using HIC. The LA-02 trial did not specify baseline liver histology for all participants, so it is improbable that the risk of progression of liver fibrosis identified in LA-03 data could be identified in LA-02 data or, for that matter, in LA-06 data.

The purpose of the LA-02 trial was stated to participating patients in the “Informed Consent Form” appended to the protocol:

[S]tudies* have shown that L1 may reduce iron overload in the heart and the liver in patients receiving regular transfusions. Further studies are required to prove the efficiency of the drug. The purpose of this [LA-02] study is to determine the safety of L1 in the treatment of iron overload.³⁹

In summary, the available documentary record shows that the short-term safety trial, LA-02, and the non-randomized long-term efficacy and safety trial, LA-03, were supportive studies for the randomized, comparison trial, LA-01. Therefore, it is hard to believe Apotex’s later claim that LA-02 was the pivotal trial.

*It appears from the Literature section of the LA-02 protocol that this was a reference to L1 trials that had been ongoing in Toronto, London and elsewhere for several years (some of which had been underway prior to Apotex acquiring commercial rights to the drug).

V. APOTEX'S 1998 ALLEGATIONS TO HSC

The adverse findings by Dr. Olivieri on L1 were based on HIC and liver histology data, both dependent on liver biopsy. After Dr. Olivieri identified the risk of progression of liver fibrosis in early February 1997, Apotex made discrediting statements about the procedure of liver biopsy. It also made allegations to HSC Pediatrician-in-Chief Dr. O'Brodovich that Dr. Olivieri's monitoring of patients on L1 during the post-trial, EDR period, constituted unauthorized research. The monitoring to which Apotex specifically referred was the determination of patients' hepatic iron concentrations (HIC) from biopsy specimens. Subsequently, in the Medical Advisory Committee proceedings, Dr. Koren and Dr. O'Brodovich made allegations against Dr. Olivieri's use of liver biopsy similar to those made by Apotex. (See sections 5P and 5Q for details and citations.)

In late August 1998, Apotex repeated its allegations of significant protocol violations to HSC President Mr. Strofolino.⁴⁰ The HSC Executive immediately repeated this allegation, without any investigation, in a widely distributed memo.⁴¹ (See section 5L(8).)

VI. DR. OLIVIERI'S INTERVENTION IN EUROPE

Having learned of the contents of some of Apotex's submissions to regulators, Dr. Olivieri contacted the regulatory agencies in Canada and in Europe in the spring of 1999 to express concerns and make allegations. She reported to us that these were as follows: (i) L1 had not yet been proven sufficiently safe and effective to warrant licencing; (ii) LA-01, not LA-02, was designed as the pivotal trial; (iii) the allegations by Apotex against her scientific procedures and results ("protocol violations") were, except possibly for immaterial instances, unfounded; and (iv) Apotex had failed to comply with regulatory requirements to submit complete and accurate information. Subsequently, in August 1999, Apotex was granted a marketing authority by the European regulatory agency for L1 under the trade name Ferriprox.^{42*} This was the first marketing authority granted for L1 in any jurisdiction, except India,⁴³ but it was restricted to "exceptional circumstances." Namely, only "thalassemia patients for whom deferoxamine therapy is contra-indicated or who present serious toxicity with deferoxamine therapy" should receive it.⁴⁴ A precautionary leaflet was to be included in the packaging:

because of the fact that in the present state of scientific knowledge, *comprehensive information on the safety and efficacy of the medicinal product cannot be provided.*⁴⁵ (emphasis added)

*L1 had been called by other names, such as Deferrum and Exferrum in Apotex submissions to other regulatory agencies.

Despite the precautionary warning required by the European regulators, Dr. Spino said in an Apotex press release that:

Ferriprox™ has been thoroughly tested in thalassemia patients in Europe and North America. The results from clinical studies have demonstrated this drug to be a safe and effective second line therapy.⁴⁶

This licence caused concern to some hematologists, and a leading specialist, Dr. David Nathan, said:

I'm disappointed. The exceptional circumstances will be violated left, right and centre. You can't possibly regulate them. The drug needs to be re-explored. There are too many doubts about its efficacy and toxicity.⁴⁷

In late 1999, Dr. Olivieri filed an application for judicial review of the licencing decision by the regulatory agency of the Commission of the European Communities. The European Court of Justice agreed to hear her application to have the licencing decision quashed, and granted intervenor status to Apotex. A hearing was held in February 2000 by the Court on two requests by Dr. Olivieri: for an interim injunction against the marketing of L1, pending a full review of the licencing decision on its merits; and for an order quashing the decision. The Court issued a preliminary judgment on April 7, 2000, denying the requested injunction, but agreeing that the main case, on the merits, could proceed.⁴⁸

Dr. Olivieri reported to us that as a result of the European Court's decision, she gained access to the specifics of Apotex's allegations that she allowed or committed serious protocol violations in the LA-01 and LA-03 trials. Thus, for the first time, she had an opportunity to review the detailed allegations, and to make a detailed, comprehensive response. These matters are still before the court at the time of this writing. We were informed that, pending their introduction in a hearing of the Court, submissions are unavailable other than to parties and intervenors, hence unavailable to this Inquiry.

(5) Consultations with Dr. Brill-Edwards

Dr. Olivieri arranged to meet with the Canadian regulatory agency (HPB) on June 30, 1999 to express her views in regard to Apotex's licencing submission to HPB. Among those accompanying her was Dr. Michèle Brill-Edwards, a pediatrician and an expert in drug development and Canadian drug regulatory law. For a decade (1986–1996) she held positions as a medical evaluator and administrator in the Health Protection Branch. Prior to that, in the mid-1980s, she worked in the same Division at the Hospital for Sick Children where Dr. Spino and Dr. Koren worked. At various times during the L1 trials and resulting controversy, Dr. Brill-Edwards was approached for advice and assistance independently by each of Dr. Spino,

Dr. Olivieri, and Dr. Koren. Each of them invited Dr. Brill-Edwards to consider employment with him or her. On the basis of her assessment of the facts and events, in 1998 Dr. Brill-Edwards decided to support Dr. Olivieri and has done so in various ways since then.⁴⁹

Dr. Olivieri first consulted Dr. Brill-Edwards in the late 1980s, about the possibility that L1 might be therapeutic for patients who were non-compliant with deferoxamine treatment.⁵⁰

Dr. Brill-Edwards advised Dr. Olivieri regarding the regulatory means to provide the drug for open treatment of non-compliant patients through the Emergency Drug Release (EDR) Program, and later, how to satisfy the requirements of the *Food and Drugs Act* for the conduct of a physician sponsored clinical trial.⁵¹

This trial was Dr. Olivieri's original pilot study of L1 funded through successive grants by MRC until 1993, after which it was continued as the LA-03 trial.

In March 1996, two months before Apotex terminated the trials in Toronto, Dr. Spino contacted Dr. Brill-Edwards "to discuss his concerns that Dr. Olivieri was taking an unduly adverse approach to the interpretation of data relating to L1." Dr. Brill-Edwards reported that Dr. Spino said he suspected that Dr. Olivieri "had a research relationship with the manufacturer of a competitor product, and so was unfairly biased ... against L1" and "that she wanted use of L1 to stop."^{52*} In this discussion, Dr. Spino indicated that Apotex would be interested in engaging Dr. Brill-Edwards as a paid consultant "on this and other [drug development] matters."⁵³

The L1 dispute attracted widespread media attention following the publication of Dr. Olivieri's article in the *New England Journal of Medicine* on August 13, 1998. On September 2, 1998 the *Globe and Mail* published a letter by Dr. Brill-Edwards, supportive of Dr. Olivieri and calling for an investigation into the matter. After this, Dr. Spino contacted Dr. Brill-Edwards on three occasions (September 7, 25 and 27, 1998). Each time he alleged that Dr. Olivieri had committed serious protocol violations in the Toronto trials (LA-01 and LA-03) and said this was why Apotex had terminated the trials. He also told Dr. Brill-Edwards that Apotex had advised government regulators that the protocol violations were serious.⁵⁴

*These allegations in March 1996 by Dr. Spino against Dr. Olivieri constitute his earliest attempt to discredit her that this Inquiry has on record. They are consistent with his later written comment to Dr. Brittenham on June 17, 1996, that Dr. Olivieri did not "believe (that L1) works." These comments are incorrect and misleading. For example, the report of Dean Aberman from his mediation meeting of June 7, where Drs. Spino and Brittenham were present, says: "Nancy wanted to continue the L1 trial for two reasons—to continue the study of effectiveness/loss of effectiveness and ensure patients on L1 would continue receiving the drug."

On September 25, 1998, Dr. Koren approached Dr. Brill-Edwards. She recorded that he suggested to her that “[she] should urge Olivieri and her supporters not to pursue a public investigation of L1 events because what would come out would severely damage Dr. Olivieri.”⁵⁵ By this point, the Naimark Review was underway. During the course of that Review Dr. Koren provided incorrect information damaging to Dr. Olivieri. During the same period he began sending his series of anonymous letters disparaging her and her supporters. It was, ironically, a further approach Dr. Koren made to Dr. Brill-Edwards (in 1999) that resulted in proof that he had written the anonymous letters.

(6) An unsigned letter by Dr. Grinstein & a signed letter by Dr. Koren

During the meeting on June 30, 1999 in Ottawa with Assistant Deputy Minister Dr. J. Losos and HPB staff, Dr. Brill-Edwards took an active part with Dr. Olivieri in going over with the government officials their responsibilities under the *Food and Drugs Act and Regulations*.⁵⁶ Five days after this meeting, on July 5, 1999, an anonymous, typed letter was mailed to Dr. Brill-Edwards. The letter opened with an incorrect statement about the licencing status of L1: “Deferiprone (L1) has been approved by the FDA.” It concluded with the suggestion that persons who supported Dr. Olivieri’s position on L1 were “demagogues and professional agitators.”⁵⁷

On July 11, 1999 Dr. Koren sent an unsolicited, handwritten and signed letter to Dr. Brill-Edwards on the letterhead of the HSC Division of Clinical Pharmacology and Toxicology, which listed him as the Director. In it he inquired about her “availability/interest” in either of “two potential options for upcoming jobs for a pediatric-pharmacologist here.” The letter concluded with a request that she call him at either of two HSC telephone numbers for his Division.⁵⁸

Dr. Brill-Edwards interpreted these letters, both of which were sent to her so soon after the meeting with HPB, as being intended, using two different approaches, to influence her to desist from supporting Dr. Olivieri’s position on Apotex’s licencing application.⁵⁹ She initially thought that Dr. Koren might be the author of both letters, since she knew Dr. Koren was under investigation by HSC as the alleged author of the series of anonymous letters against Drs. Olivieri, Durie, Chan and Gallie, although he denied responsibility. She found being the recipient of an anonymous letter disturbing.⁶⁰

Dr. Brill-Edwards decided to contact Dr. Koren to clarify his purpose. In late August she had two discussions with him. He described the “potential options for upcoming jobs” in his Division she might fill, but he also raised

another matter. He told Dr. Brill-Edwards that she was respected by people on both sides of the L1 controversy, including him, and he suggested that she act as mediator between him and Dr. Olivieri and her supporters, to help in resolving their differences. Upon reflection, she concluded that this was not a situation where mediation was an appropriate approach, and she did not wish to be considered for employment in a Division headed by him. Subsequently Dr. Brill-Edwards decided to support Dr. Olivieri's position on the licencing of L1. She appeared at a press conference with her in October 1999, in Ottawa, when Dr. Olivieri had a second meeting with HPB about the Apotex licencing application.⁶¹

In the fall of 1999, when her support for Dr. Olivieri in the L1 controversy was well known, Dr. Brill-Edwards applied for a position of clinical associate in the hemoglobinopathy clinic in The Toronto Hospital, directed by Dr. Olivieri. She was interviewed by Dr. Armand Keating, Dr. Olivieri's Division Chief in November, was offered the position and began work early in 2000.⁶²

Dr. Koren continued to lie to HSC's harassment investigator, Ms. Humphrey, about his authorship of the series of anonymous letters, until December 1999. In the autumn of 1999, because Ms. Humphrey's investigation had been continuing for months with no completion date having yet been indicated, Drs. Gallie, Olivieri, Durie, Chan and Dick decided to have DNA tests done on the saliva residues on the envelopes of the anonymous letters. They had already accused Dr. Koren of being the author and had provided substantial forensic evidence to the Hospital and the University in May, 1999, in response to which the Hospital launched its own investigation. The possibility of using DNA evidence had occurred also to Ms. Humphrey. Both she and Dr. Gallie *et al.* needed a DNA sample known to be Dr. Koren's for comparison. Dr. Koren refused to provide one to Ms. Humphrey.⁶³ It occurred to Dr. Chan that the envelope that contained Dr. Koren's signed letter to Dr. Brill-Edwards might provide a saliva sample.⁶⁴ Dr. Brill-Edwards agreed to provide the envelope and letter to Dr. Gallie *et al.* for this purpose. The result of the DNA test (obtained from Helix Biotech Laboratories on December 7, 1999) was clear: Dr. Koren was the author of the anonymous letters (issued between October 1998 and May 1999) against Drs. Olivieri, Durie, Chan and Gallie.⁶⁵ Dr. Koren was informed of this result and he subsequently admitted responsibility.

However, DNA from the envelope of the anonymous letter of July 5, 1999 to Dr. Brill-Edwards did not match Dr. Koren's DNA. Since it was postmarked in Toronto, and referred to HSC and to the licencing of Apotex's drug L1, Dr. Brill-Edwards began to consider other possibilities among HSC staff. She hypothesized that it had to be someone who had supported the position of the

HSC Executive and the position of Apotex. In October 1998 Dr. Brill-Edwards had received a signed letter from Dr. Sergio Grinstein,⁶⁶ a Senior Scientist in HSC and holder of the Pitblado Chair in Cell Biology (a joint University-Hospital Chair). This letter criticized her for her letter published by the *Globe and Mail* on September 2 of that year, in which she had called for an “independent investigation” into the Hospital’s failure to support Dr. Olivieri against the actions of Apotex. Dr. Grinstein had publicly taken the part of the Hospital administration in the L1 controversy and repeated his views to Dr. Brill-Edwards in his signed letter to her.⁶⁷ Dr. Brill-Edwards had a DNA test done on the envelope that contained this signed letter and a comparison with the anonymous one she had received. The result was clear: Dr. Grinstein was the author of the anonymous letter of July 5, 1999.⁶⁸

Dr. Brill-Edwards made a formal complaint about Dr. Grinstein to Dean David Naylor of the Faculty of Medicine, University of Toronto.⁶⁹ When confronted, Dr. Grinstein admitted being author of the anonymous letter, as was reported in the national and international press.⁷⁰ Dean Naylor subsequently circulated a memo advising medical staff that he had called Dr. Grinstein to a meeting and “admonished” him for his conduct in sending the anonymous letter to Dr. Brill-Edwards.⁷¹

(7) Conclusions

1 | Changes to the Canadian *Food and Drugs Act* and *Regulations* are needed to ensure that:

- Industrial sponsors of drug trials (or holders of commercial rights to a drug) are prohibited from taking any action to impede a clinical investigator (or a treating physician) from informing trial participants (or patients), or others with a right or need to know, of any unexpected risk that may be identified during a trial (or after the termination of a trial or trials).
- In the event of premature termination of a trial by an industrial sponsor, the Health Protection Branch is required to investigate the circumstances promptly, and then to act robustly to protect the public interest.
- In the event of serious allegations by an industrial sponsor against a clinical investigator, the Health Protection Branch is required to disclose the allegations to the investigator and provide the investigator with a full and fair opportunity to respond.

2 | After Apotex prematurely terminated the Toronto trials and Dr. Olivieri subsequently published her findings of serious risks of L1 identified in data from these trials, Apotex sought to have the drug licenced primarily on the basis of a short-term safety trial. It claimed that this (LA-02) trial was the pivotal trial, a claim that is hard to believe in light of the available documentation.

In 1999 Apotex was granted a marketing licence in the European Communities under restricted conditions. We have not been informed of any marketing licences for L1 granted to Apotex in Canada, the USA, Australia or elsewhere.

3 | A significant aspect of Apotex's licencing submissions for L1 involved allegations discrediting to Dr. Olivieri and her work. Similar allegations were later prominent in events at HSC.

4 | The two HSC scientists who wrote anonymous letters against Dr. Olivieri and her supporters, Dr. Koren and Dr. Grinstein, were identified by DNA evidence they inadvertently provided to Dr. Brill-Edwards shortly after she had assisted Dr. Olivieri in making a presentation to the Canadian regulators on Apotex's efforts to obtain a marketing licence for L1.

Notes

Notes to Chapter 2: Background information

1. D.J. Weatherall and J.B. Clegg, *The Thalassemia Syndromes*. 3rd ed. Blackwell Scientific, Oxford (1981), p. 686; also, A. Cohen *et al.*, *Cooley's Anemia*, NIH progress report on science and treatment (1995), p. 22.
2. D.J. Weatherall and J.B. Clegg, *The Thalassemia Syndromes*. 3rd ed. Blackwell Scientific, Oxford (1981), p. 217; N.F. Olivieri, review article, "The β -Thalassemias," *The New England Journal of Medicine*, 341, 2 (July 8, 1999), p. 104.
3. N.F. Olivieri and G.M. Brittenham, review article, "Iron-chelating therapy and the treatment of thalassemia," *Blood, the Journal of the American Society of Hematology*, 89, 1, (Feb. 1, 1997), p. 750.
4. A. Cohen *et al.*, *Cooley's Anemia*, NIH report (1995), p. 23.
5. E. Angelucci *et al.*, "Needle liver biopsy in thalassemia," *British Journal of Haematology*, 89 (1995), pp. 757–761.
6. N.F. Olivieri and G.M. Brittenham, review article, "Iron-chelating therapy and the treatment of thalassemia," *Blood, the Journal of the American Society of Hematology*, 89, 1, (Feb. 1, 1997), tables 3 and 4, pp. 748–9.
7. D.G. Nathan, *Genes, Blood and Courage*. Belknap/Harvard, Cambridge, Mass. (1995).

Notes to Chapter 3: Policy context

1. M.C. Bassiouni, T.G. Baffes & J.T. Evard, "An Appraisal of Human Experimentation in International Law and Practice: The Need for International Regulation of Human Experimentation" (1981) 72 *The Journal of Criminal Law and Criminology* 1597–1666.
2. "The Nuremberg Code," reprinted in *Trials of War Criminals before the Nuremberg Military Tribunals under Control Council Law No. 10*, vol. 12: 81–82. Washington, DC: US Government Printing Office, 1949. Also printed in Medical Research Council of Canada, *Ethics in Human Experimentation*, pp. 59–60, 1978.
3. J. Jones, *Bad Blood: The Tuskegee Syphilis Experiment—A Tragedy of Race and Medicine* (New York: The Free Press, 1981).
4. A. Collins, *In the sleep room: the story of the CIA brainwashing experiments in Canada* (Toronto: Key Porter Books, 1997). This research was originally funded by the CIA and later was funded by the Canadian government.
5. The CBS-TV program *60 Minutes* broadcast December 19, 1999 reviewed the case of Dr. Dong, as well as the case of Dr. Olivieri.
6. *Food and Drugs Act*, R.S.C. 1985, c.F-27; *Food and Drug Regulations*, C.R.C., C. 870, s.C.08.005.
7. Arts. 18-25 C.C.Q.
8. *Halushka v. University of Saskatchewan et al.* (1965), 53 D.L.R. (2d) 436 (Sask. C.A.) [hereinafter *Halushka*].
9. *Weiss c. Solomon* (1989), 48 C.C.L.T. 280 (C.S.) [hereinafter *Weiss*].
10. Medical Research Council of Canada, *Guidelines on Research Involving Human Subjects 1987* (Ottawa: Supply and Services Canada, 1987).
11. *Good Clinical Practice: Consolidated Guideline* (Ottawa: Therapeutic Products Directorate, 1997).
12. Medical Research Council of Canada, Natural Sciences and Engineering Research Council of Canada, and Social Sciences and Humanities Research Council of Canada, *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans* (Ottawa: Medical Research Council of Canada, 1998).
13. *Ibid.* at i.1.

14. 45 C.F.R. 46 (2000).
15. 21 C.F.R. 50 (2000).
16. World Medical Association, *Declaration of Helsinki* (2000), online: World Medical Association, Inc. <<http://www.wma.net/e/approvedhelsinki.html>>.
17. *International Ethical Guidelines for Biomedical Research Involving Human Subjects* (Geneva: CIOMS, 1993).
18. F. Baylis *et al.* eds., *Health Care Ethics in Canada* (Toronto: Harcourt Brace, 1995) at 322.
19. *Supra* note 5.
20. *Supra* note 11.
21. *Ibid.* at 1.1.
22. *Ibid.* at 7.1–7.6.
23. *Ibid.* at 3.4–3.5.
24. Excerpts from *TCPS* on researchers' responsibilities:

As a condition of funding, we require, as a minimum, that researchers and their institutions apply the ethical principles and articles of this policy.

This Policy addresses the interdependent duties to research subjects, that are shared by researchers, institutions and Research Ethics Boards (REBS).

In certain situations, conflicts may arise from application of these principles in isolation from one other. Researchers and REBS must carefully weigh all the principles and circumstances involved to reach a reasoned and defensible conclusion.

However, researchers and institutions also recognize that with freedom comes responsibility, including the responsibility to ensure that research involving human subjects meets high scientific and ethical standards. The researcher's commitment to the advancement of knowledge also implies duties of honest and thoughtful inquiry, rigorous analysis, and accountability for the use of professional standards. Thus, peer review of research proposals, the findings and their interpretation contribute to accountability, both to colleagues and to society.

In a research team, the principal researcher is ultimately responsible for the actions of those acting with delegated authority.
25. *Ibid.* at 1.2–1.3, 4.2.
26. *Ibid.* at i.1.
27. *Ibid.* at i.2.
28. *Supra* note 9 at 43.
29. *Ibid.* at 52.
30. *Supra* note 11 at i.1.
31. *Ibid.* at 7.4. See also p. 4.1 at para. 5.
32. *Ibid.* at 2.5–2.6.
33. *Ibid.* at 2.6.
34. *Ibid.*
35. *Ibid.* at 7.5.
36. *Ibid.* at i.8 (emphasis added).
37. *Ibid.* at 4.2.
38. See B.A. Brody, "Conflicts of Interests and the Validity of Clinical Trials", in *Conflicts of Interest in Clinical Practice and Research*, Roy G. Spece *et al.*, eds (New York: Oxford University Press, 1996) pp. 407-417.
39. *McKinney vs. University of Guelph*, 3 *Supreme Court Reports* (1990).
40. Majority decision by Supreme Court of the United States, in *Keyishian c. Board of Regents*, 385 US 589 (1967), p. 174.
41. Public statement by Prichard on the Olivieri case, 981209.
42. Policy Statements on Academic Freedom: CAUT (May 1977) and AUCC (May 1988).
43. *Tri-Council Policy Statement for Ethical Conduct of Research Involving Humans*,

Context, Section E, “Academic Freedoms and Responsibilities,” published by CIHR, NSERC and SSHRC (1998, updated 1999).

44. Memorandum of Agreement between the Governing Council of the University of Toronto and the University of Toronto Faculty Association, dated 770628, consolidated with subsequent amendments, 980616.
45. R. Hofstadter and W. P. Metzger, *The Development of Academic Freedom in the United States*, Columbia U. Press (1955); also R. Hofstadter and W. Smith, *American Higher Education*, volume II, U. Chicago Press (1961).
46. E.W. Schrecker, *No Ivory Tower*, Oxford U. Press (1986).
47. G.H. Hardy, *Bertrand Russell and Trinity*, Arno Press (1977), reprinted from Cambridge U. Press (1942).
48. H.M. Kallen and John Dewey, *The Bertrand Russell Case*, Viking Press (1941); and P. Edwards, appendix to B. Russell, *Why I Am Not a Christian*, Simon & Schuster (1957).
49. B. Russell, *The Autobiography of Bertrand Russell*, vol. 3, page 30, McClelland and Stewart (1969).
50. M. Horn, *Academic Freedom in Canada*, U. Toronto Press (1999).
51. V.C. Fowke (Chair) and B. Laskin, “Report of the investigation ... into the dismissal of Professor H.S. Crowe ...,” *CAUT Bulletin*, 7, 3 (1959), pp. 3–50 (plus appendices).
52. D.A. Soberman, *CAUT Bulletin*, 13, 3 (1965), pp. 5–36.
53. *McKinney vs. University of Guelph*, 3 *Supreme Court Reports* (1990), 229.
54. *McKinney vs. University of Guelph*, 3 *Supreme Court Reports* (1990).
55. Memo, Evans to Thompson (CoI), 991125.
56. Naimark Report, p. 123.

Notes to Chapter 4: The context of associations between the University of Toronto & Apotex Inc.

1. Report number 90 of the Academic Board, 981008.
2. Minutes, Governing Council, 981217.
3. Naimark Report, p. 16, footnote.
4. Article in *Toronto Star*, 990904; article in the *University of Toronto Magazine*, Autumn 1998, p. 10; article in *The Varsity*, 991109; and Report number 90 of the Academic Board, 981008.
5. Memo, Lister to Naimark, 981030.
6. Article, *Toronto Star*, 990904, quoting University Vice-President Dellandrea.
7. Article, *Toronto Star*, 990904.
8. Article, *Globe & Mail*, 990916.
9. Letter, Spino to Hindmarsh (Dean of Pharmacy), 980924; and letter, O’Brien (Pharmacy) to Spino, 980413.
10. Letter, Spino to Hindmarsh (Dean of Pharmacy), 980924.
11. Naimark Report, p. 16-17; and letter, Koren to Buchwald, 980501.
12. Letter, Koren to Buchwald, 980501, N 363 (not archived).
13. Letter, Durie to Buchwald, 980504, N 367 (arch 206).
14. Petition letter by Durie, Dick and fifty others to Buchwald, 980626.
15. Letter, Olivieri to Becker (Chair, MAC), 980402.
16. Letter, Koren to Becker (Chair, HSC Medical Advisory Committee), 980415, N 351 (arch 199).
17. Letter, Koren to Becker (Chair, HSC Medical Advisory Committee), 980415, N 351 (arch 199).
18. Letter, Spino to A. Klein (Health Canada), 960813; and Priority Review Submission by Apotex Research Inc. to Health Canada, 970930.
19. Letter, Spino to Koren, 971023, N 312 (not archived).

20. Letter, Hudgins (UTFA) to Naylor (Dean of Medicine), 991217, enclosing copy of web pages.
21. Naimark Report, p. 16.
22. Letter, Gallie to Buchwald and Strofolino, 980603.
23. Memo, Lister to Naimark, 981030.
24. Minutes, Governing Council, 981217.
25. Article, *Toronto Star*, 990904 and report number 317 of the UT Executive Committee, 990907.
26. Report number 317 of the UT Executive Committee, 990907.
27. Article, *Toronto Star*, 990904.
28. Report number 317 of the Executive Committee, UT, 990907.
29. See also: article, the *Varsity*, 991109; and article in the *University of Toronto Magazine*, Autumn 1998, p. 10.
30. Report number 317 of UT Exec. Comm., 990907. See also minutes of Gov. Council, 990916; and articles, *Globe and Mail*, 990916 and *UT Bulletin*, 990921.
31. Minutes, Governing Council, 990916.
32. Article, the *Varsity*, 991109.
33. UT annual report, *Globe&Mail* insert, December 2000.

Notes to 5A: The Toronto L1 Trials

1. Olivieri's 1988 MRC application.
2. The October 1990 application by Olivieri and Koren to MRC for renewal of funding for the pilot study includes pharmacokinetic work, among many other objectives— see Olivieri's MRC application file. Dr. Olivieri and Dr. Koren had earlier collaborated on studies of the standard iron-chelation drug, DFO, which involved pharmacokinetics, for instance, in the article, Y. Bentur, G. Koren, N.F. Olivieri *et al.*, "Comparison of desferrioxamine pharmacokinetics in thalassemia children exhibiting neurotoxicity and asymptomatic patients," *Clin. Pharmacol. Ther.*, 47 (1990), pp. 478–82.
3. Olivieri's MRC application file. Specifically: i) Olivieri applied to MRC in September 1988 for a two-year grant for the pilot study and the application was successful, a two-year grant being awarded for 1989–1991; ii) she applied to MRC in October 1990 for a three-year grant to continue the pilot study to study long-term efficacy, and was granted a one-year "continuing grant" for July 1991–June 1992; iii) she applied to MRC in October 1991 for a much larger five-year grant to mount a new randomized trial. This last application was not successful and instead MRC awarded a one-year "terminal grant." Since there was no randomized trial then, and there would not be a randomized trial until 1993, the interpretation was that the "terminal grant" could be used either to phase out the pilot study in one more year, or to continue that study and the L1 program for another year while other sources of funding were sought.
4. REB protocol-approval form for continuation of the pilot study, 900329.
5. Liver biopsy and HIC are discussed in the March 1990 protocol application by Dr. Olivieri to the HSRC (REB) dated March 1990, and in the October 1990 application by Olivieri and Koren to MRC for renewal of funding for the pilot study.
6. Timetable for the pilot study, October 1990 application to MRC, p. 11.
7. Information and consent forms for the pilot study, 1990.
8. Regarding the 1991 meeting, see letter and attachment (listing participants) re: meeting on 910812 with FDA for "pre-IND" discussion of L1; participants included S.B. Fredd and 4 other FDA staff, D.G. Badman and A.S. Levine of NIH, and N.F. Olivieri and G.M. Brittenham and 4 other American investigators. Regarding the 1993 meeting, see the review article by N.F. Olivieri and G.M. Brittenham in *Blood*, 89, 3 (1997), page 753. For a summary of Fredd's advice, see Olivieri's brief to MAC dated 981012, page 16.
 - b) Regarding Apotex involvement, see memo, Spino (Apotex) to other Apotex staff,

940625 reviewing organizational meetings for the LA-02 trial. Dr. Spino wrote, “A decision was made [by Apotex] to prepare a Regulatory submission for the US and other parts of the world. The groundwork for this had already been done in preliminary meetings with FDA and a group of hematologists headed up by Gary and Nancy. NIH was expected to provide funding. Eventually it was agreed that FDA would support a trial of L1 in thalassemics if there was an appropriate sponsor (pharmaceutical company), an acceptable formulation and the proposed protocol met the requirements of the FDA. Apotex agreed to take on the role of pharmaceutical sponsor, but in doing so it assumed it would then control the development of the drug.”

9. See the review article by N.F. Olivieri and G.M. Brittenham in *Blood*, 89, 3 (1997), page 753; and Olivieri’s brief to MAC dated 981012, p. 16.
10. G.M. Brittenham *et al.*, *New England Journal of Medicine*, 307 (1982), pp. 1671–5; see also Brittenham’s Statement dated 990327 submitted to MAC by Olivieri on 991012. There is now a second laboratory, in Germany, with equipment similar to that of Dr. Brittenham.
11. Olivieri’s MRC application file—letter, Slotin (MRC) to Olivieri, 920625.
12. Olivieri’s MRC application file—letter dated 921008 by Slotin (MRC) to Nathan (Harvard) who had written to inquire about the reasons for not funding the randomized trial, said that Olivieri was invited to “resubmit” an application to MRC taking into account comments made “in the reviews” by MRC reviewers. One of these suggested Dr. Olivieri re-apply under MRC’s university-industry program.
13. Memo, Spino (Apotex) to other Apotex staff, 940625, p. 3.
14. Contract for the LA-01 trial, between Apotex and Olivieri and Koren, dated 930423.
15. Letter, Olivieri to Spino, 960206, copied to Koren.
16. Olivieri’s CV.
17. Letter, Olivieri to Spino, 960206, copied to Koren.
18. Letter, Koren to Woloski (Apotex), 930322. Dr. Koren typed “contact” instead of “contract” but from the full text of the letter and all other relevant documentary evidence (for instance, the subsequent LA-01 contract specified that the Apotex funds would go into Dr. Koren’s research accounts), the only reasonable interpretation is that this was a typographical error. Typographical and spelling errors are not uncommon in letters written by Dr. Koren and available to this Inquiry.
19. Contract for the LA-01 trial, between Apotex and Olivieri and Koren, dated 930423.
20. Ethical approval form to notify MRC, dated May 18, 1993, page 733 of Olivieri MRC file.
21. Olivieri’s MRC application file—May 1993 application. The application to MRC for funding for the LA-01 trial also listed Dr. T. Einarson, an associate professor of pharmacy in the University of Toronto as a co-investigator, but he did not have a prominent role in later events.
22. Olivieri’s MRC application file—May 1993 application.
23. Clause 3 (iv) of the LA-01 contract, 930423.
24. Letter, Christian (HSC) to Glasenberg (Apotex), 960705, concerning review of accounting records.
25. Letter, Koren to Woloski (Apotex), 930322. It is of note that neither this informal letter of March 1993 nor the formal LA-03 contract of October 1995 gave Apotex any ownership or confidentiality rights to the LA-03 data.
26. Dr. Koren’s letter dated 930322 to Woloski (Apotex) was mainly about the LA-01 trial. The funding discussed in it proposed a budget of \$128,000/year as the Apotex share of the costs for the proposed LA-01 trial. This same amount was specified in the LA-01 contract signed a month later, on April 23, and again specified as the contribution of the industrial sponsor in the subsequent application for the MRC contribution to the randomized, comparison trial (LA-01).
27. LA-01 Protocol (dated May 1993, last Revised: October 5, 1995), p. 11.
28. Application to MRC for the randomized trial, signed by Olivieri and Koren and endorsed by Haslam and others, May 1993.

29. LA-01 Protocol (dated May 1993, last Revised: October 5, 1995).
30. LA-03 contract, signed and issued by Spino on 951002, and signed by Koren 951010 and Olivieri 951012.
31. LA-01 contract, 930423.
32. LA-01 Protocol (Revised: October 5, 1995), pp. 20 and 25.
33. Interview of Olivieri broadcast by the CBS-TV program *60 Minutes*, 991219.
34. Naimark Report, p. 107. A similar comment was made in point 3 of a public statement by the University's 12-point statement of December 3, 1998.
35. University of Toronto Publication Policy, Feb. 27, 1975—in force at all relevant times in this case, until March 2001 when a modification was announced.
36. Naimark Report, p. 21. Similar point made in the HSC Research Policy Review Task Force Report at p. 23.
37. In a letter dated 23 July 1998, Dr. Fred Saunders, a researcher at HSC wrote to Dr. Manuel Buchwald, Chief of Research and Director, Research Institute, HSC, informing him that, "I have recently signed a contract with Sangstat (also signed by Anne Marie Christian [Associate Director, Administration and Planning, Research Institute, HSC]) that gives the company complete control over a study of ATG in graft vs host disease." He also noted that, "They can change the protocol at will and have veto power over all publications and presentations." (See section 5 L.)
38. *Toronto Star*, 010327, citing Dean Naylor.
39. Letter, Koren to Woloski (Apotex), 930323.
40. Naimark Report, p. 103.
41. Naimark Report, p. 103.
42. Contract for LA-03 issued and signed by Apotex on 951002, and signed by Koren on 951010 and Olivieri on 951012
43. Revised protocol, LA-01, 951005 (first approved 930518).
44. Revised protocol, LA-03, 950927 (this was first approved March 1991, when the extension of the pilot study beyond the initial two years, 1989–1991, and this protocol replaced the one approved in 1990, at the outset of the longer-term phase of the pilot study).
45. LA-01 contract, dated 930423.
46. LA-03 contract, October 1995 (signed by Spino, Koren and Olivieri on Oct. 2, 10 and 12, resp.).

Notes to 5B: Designing the international trial

1. Article, N.F. Olivieri *et al.*, *New England Journal of Medicine*, 332, 14 (April 6, 1995), p. 922.
2. Letter, Spino to Olivieri, 960214.
3. Memo, Spino to Woloski *et al.* (of Apotex), 940625, copied to Olivieri with a covering memo, 940626.
4. LA-02 contract between Olivieri and Apotex, 950617.
5. LA-02 contract between Olivieri and Apotex, 950617.
6. University of Toronto Publication Policy, Feb. 27, 1975.
7. Naimark Report, p. 25. There is a similar statement at p. 100 of the Naimark Report.
8. Apotex Research document, "Comprehensive Summary—Exferrum," 980130, prepared in connection with submission to Australian regulators, pp. 50–51. "Exferrum" is an Apotex term for LI.
9. LA-02 protocol, dated 940630, as modified on 950721.
10. LA-02 protocol, dated 940630, as modified on 950721, Appendix A.
11. Document prepared for regulatory purposes by Apotex Research, titled, "Comprehensive Summary—Exferrum," 980130, p. 78.

Notes to 5C: Progress of the Toronto trials

1. Article, N.F. Olivieri *et al.*, “Iron-chelation therapy with oral deferiprone in patients with thalassemia major,” *NEJM*, 332, 14 (April 6, 1995), pp. 918–922.
2. Contract for LA-01, 930423; protocol for LA-01(section 5.2), 951005, and letter, Koren to Woloski (Apotex), 930322.
3. Brief, Olivieri to MAC, 991012, p. 18.
4. Originally Dr. R. Hutcheon was the site supervisor in Montréal, but he was later replaced by Dr. Dougherty, see Apotex “Statement of Defence and Counterclaim,” 000619, par. 17.
5. Letter, Koren to Zlotkin (REB), 950911 (see also letter, Olivieri to Zlotkin, 950918).
6. Letter, Olivieri to Zlotkin, 950918.
7. Letters: Koren to Spino, 050817 and Olivieri to Spino, 950829.
8. Naimark Report, p. 30.
9. Letter, Olivieri to Spino, 960520, with draft budget attached.

Notes to 5D: Concerns arising in 1995

1. Brief, Olivieri to MAC, 991012, p. 19; and letter, Olivieri to A. Klein (HPB), 950620.
2. Brief, Olivieri to MAC, 991012, p. 19; letter, Spino to Olivieri, 970307, and testimony of Olivieri to CoI.
3. Letter, Spino to Olivieri, 950307.
4. Letter, Olivieri to Spino, 950307, replying to Spino’s letter of the same date.
5. Letter, Olivieri to Spino, 950307.
6. Draft revision to LA-03 protocol dated 950428, prepared and signed by seven Apotex staff members between 950428 and 950510.
7. Draft revision to LA-03 protocol dated 950428, prepared and signed by seven Apotex staff members between 950428 and 950510.
8. Draft revision to LA-03 protocol dated 950428, prepared and signed by seven Apotex staff members between 950428 and 950510.
9. Olivieri’s handwritten changes to the Apotex draft protocol dated 950428—written on a copy of the Apotex draft.
10. Testimony of Olivieri to CoI. See also: Apotex Research “Background Booklet,” Item 6, Clinical Experience, 960301—obtained through an application under the *Privacy Act*—in which Apotex noted that, “In mid-1995, the principal investigator (Dr. Olivieri) began taking patients off deferiprone to put them on other chelation therapy.”
11. The discussion between Dr. Olivieri and Dr. Klein was recorded in a letter, Olivieri to Klein, later the same day, 950620.
12. Letter, Olivieri to Spino, 950307.
13. Letter, Spino to Olivieri, 950308.
14. Letter, Koren to Spino, 950817 see also, letters, Olivieri to Spino, 950828, and 950829.
15. Letter, Olivieri to Spino, 950723—copied to Koren.
16. Letter, Olivieri to Spino, 950723.
17. Letter, Olivieri to Spino (copied to Koren), 950807—quotation is from an attachment.
18. Letter, Olivieri to Spino (copied to Koren), 950807—quotation is from an attachment.
19. Letter, Spino to Olivieri, 950814.
20. Letter, Koren to Spino, 950817, suggesting ways to improve communication between the investigators and Apotex and asserting that the investigators were meeting their responsibilities; see also letters cited in the following endnote.
21. Letters: Olivieri to Spino, 950828; 950829; 950908; 950915; and 950918, and Spino to Koren, 950830, and 950911.
22. Letter, Olivieri to Spino, 950915, copied to Koren, Brittenham and Zlotkin.
23. Letter, Olivieri to Spino, 950918.
24. Letter, Olivieri to Zlotkin, 950918.

25. Letter, Olivieri to Zlotkin, 950918; and testimony of Olivieri to CoI.
26. LA-03 contract, issued and signed by Spino on 951002, and signed by Koren on 951010 and Olivieri on 951012.
27. Revised LA-03 protocol, dated 950927, signed by Olivieri on 950930 and by Koren on 951010. The protocol for the long-term phase of the pilot study was dated March 1991; there was a Modification #1 dated October 1993, after Apotex began to supply L1, and the one dated 950927 was denoted Modification #2.
28. LA-03 contract, issued and signed by Spino on 951002, and signed by Koren on 951010 and Olivieri on 951012.
29. LA-03 contract, issued and signed by Spino on 951002, and signed by Koren on 951010 and Olivieri on 951012.
30. LA-03 contract, issued and signed by Spino on 951002, and signed by Koren on 951010 and Olivieri on 951012.
31. Letter, Spino to Brittenham, 951003.
32. Minutes taken by Apotex staff of meeting on 960208 with Olivieri *et al.*

Notes to 5E: Identification of the first risk

1. Draft (and final) report by Olivieri to REB, sent first to Apotex in early February 1996, then to REB after discussions with Apotex, with covering letter to Spino, 960212.
2. Minutes taken by Apotex staff of meeting on 960208 with Olivieri *et al.*
3. minutes taken by Apotex staff of meeting on 960208 with Olivieri *et al.*
4. minutes taken by Apotex staff of meeting on 960208 with Olivieri *et al.*
5. Letter, Spino to Olivieri, 960212.
6. Letter, Spino to Olivieri, 960212.
7. Letter, Spino to Olivieri, 960212.
8. Report intended for the REB—advance copy provided to Apotex with letter from Olivieri to Spino dated 960212—sent to REB by Olivieri with letter to Zlotkin on 960305.
9. Letter, Spino to Olivieri 960214.
10. Letter, Spino to Olivieri 960214.
11. Letter, Olivieri to Spino, 960215.
12. Letter, Spino to Olivieri, 960216.
13. Letter, Spino to Olivieri, 960216.
14. Letter, Olivieri to Zlotkin, 960229 .
15. Letter, Olivieri to Zlotkin, 960305 (with attached report to REB) .
16. Letter, Spino to Zlotkin, 960315, with attached copy of Apotex report, Preliminary Assessment—Apparent Variability in Therapeutic Response to Deferiprone Study LA-03.
17. Minutes of meeting, Olivieri and Zlotkin, 960325.
18. Letter, Zlotkin to Spino, 960325.
19. Letter, Zlotkin to Olivieri, 960409. In this letter, Dr. Zlotkin also directed Dr. Olivieri to submit for approval by the HSC REB a copy of the LA-02 trial protocol. He had mistakenly assumed that she was an investigator for LA-02, but the fact she was a consultant not an investigator was confirmed to him in a letter by Dr. Spino on 960502 (page 4 of that letter).
20. Letter, Spino to Koren, 960418 .
21. Naimark report, p. 121.
22. Letter, Spino to Koren, 960418.
23. Letter, Spino to Zlotkin, 960502.
24. Letter, Spino to Zlotkin, 960502.
25. Letter, Spino to Zlotkin, 960502.
26. Letter, Zlotkin to Spino, 960510.
27. Letter, Olivieri to Spino, 960520; and letter, Olivieri to Zlotkin (REB), 960520. The revised

information and consent forms are in Olivieri's 991012 submission to MAC, binder II, tabs 29 and 33.

28. Letter, Olivieri to patients and parents, accompanying revised information and consent forms, dated May 10, 1996, but provided to recipients later, with the forms—Olivieri's 991012 submission to MAC, binder II, tab 29.
29. Letter, Spino to Olivieri, 960214.
30. Letter, Spino to Zlotkin, 960502.

Notes to Section 5F: Trial terminations and legal warnings

1. Letter, Spino to Olivieri, 960508.
2. Letter, Spino to Olivieri, 960508.
3. a) Letter, Olivieri to Spino, 960520, with draft LA-01 budget attached; and b) letter, Olivieri to Zlotkin, 960520, with revised patient information and consent forms attached.
4. Letter, Spino to Olivieri and Koren, 960524.
5. Letter, Spino to Olivieri and Koren, 960524.
6. letter from Spino to Olivieri, 960524 .
7. Transcription of voice mail message from Spino to Olivieri - telephone call on 960524.
8. Letter, Woolcock (Apotex) to Carmen (HPB), 970225, in which he confirmed what Apotex told HPB at the time when it terminated the trials in May 1996.
9. Letter, Spino to Brittenham, 960617.
10. B. Freedman, "Equipoise and the ethics of research" (1987) 317 *The New England Journal of Medicine* 141-5.
11. E-mail, Aberman to Durie *et al.*, 980830.
12. Letter, Spino to Olivieri, 960822.
13. Letter, Woolcock (Manager of Regulatory Affairs, Apotex) to Carmen (HPB), 970225, in which he confirmed what Apotex told HPB when it terminated the trials in May 1996; and letter, Spino to Brittenham, 960617. The Woolcock to Carmen letter was obtained by application under the *Privacy Act* and has passages expurgated by government staff.
14. Letter, Spino to editor of *The Medical Post*, 970218.
15. Letter, Spino to Olivieri, 970827.
16. Apotex regulatory submission to Health Canada, 980130. In the letter, Spino to Olivieri, 970827 (cited above), there was mention of alleged protocol violations, but this was not given as the reason for terminating the trials, namely, that quoted in the text above.
17. Apotex regulatory submission to Health Canada, dated 980126.
18. Letter, Spino to Strofino, 980831.
19. Priority Review Submission by Apotex Research Inc. to Health Canada, 970930—excerpts obtained through an application under the *Privacy Act*.
20. Letter, Spino to A. Klein (Health Protection Branch of Health Canada), 970128, obtained through an application under the *Privacy Act*.
21. Legal opinion from Daniel A. Soberman, Professor Emeritus of Law at Queen's University to Jon Thompson, Chair of Committee of Inquiry dated 21 March 2000. (See Appendix F.)
21. See also, for example, the *MRC Guidelines on Research Involving Human Subjects (1987)*, in Chapter V on "Principles of Consent" under Informed Consent at page 28:

The obtaining of informed consent is only one step in a continuing process. The educative effort commences before and continues after the signing of a document, and continuing consent must be elicited during the progress of research. ...

According to the US Department of Health and Human Services (DHHS), the DHHS requires as part of ongoing disclosure that "when appropriate ... the following ... information shall also be provided ... A statement that significant new findings developed during the course of research which may relate to the subject's willingness to

continue participation will be provided to the subject (Section 46.116(b)),” as cited in R.J. Levine, *Ethics and Regulation of Clinical Research*, 2d ed. (New Haven and London: Yale University Press, 1988) at 118. In addition, the CIOMS Guidelines requires continuing consent and for subjects to be informed of “... any new information [that] may have come to light, either from the study or from outside the study, about the risks or benefits of therapies being tested or about alternatives to the therapies.” [See Guideline 3—Obligations of investigators regarding informed consent] as cited in Z. Bankowski & R.J. Levine, eds., *Ethics and Research on Human Subjects - International Guidelines* (Geneva: Council for International Organizations of Medical Sciences (CIOMS), 1993) at 18.

Notes to Section 5G: Post-termination events

1. Letter, Olivieri and Koren to Haslam, 960525.
2. E-mail, Aberman to Durie *et al.*, 980830.
3. E-mail, Aberman to Durie *et al.*, 980830—this e-mail said that the mediation meeting was on June 6—a typographical error—the meeting was on June 7, 1996.
4. Notes strategy in preparation for the mediation meeting of June 7, drafted by CMPA for Dr. Olivieri.
5. E-mail, Aberman to Durie *et al.*, 980830.
6. E-mail, Aberman to Durie *et al.*, 980830.
7. Letters: Koren to O’Brodivich, 971126; and Koren to Becker, 980415.
8. a) e-mail, Aberman to Durie *et al.*, 980830
b) In a letter to Dr. O’Brodivich on 971126, Dr. Koren wrote, “I served as a contact person between Dr. Olivieri and Apotex, to allow Emergency release of drug, as the two parties were not on speaking terms.”
9. Letters: Spino to Koren, 960418; Spino to Klein (HPB), 960813; and Kay (Apotex counsel) to Colangelo (CMPA counsel for Olivieri and Koren), 960814.
10. (i) Letter, Woolcock (Apotex) to Olivieri, 960627— this confirms HPB authorizations to Olivieri at HSC and Sher at TTH as treating physicians, but it is Olivieri who is asked to “report” pursuant to Section C.08.010 of the Act and Regulations, so she was “the practitioner”; this letter indicates a 90-day supply of L1 being provided; there is no mention of Dr. Koren in this letter. Dr. Graham Sher is a hematologist who had recently been a postdoctoral research fellow of Dr. Olivieri and was at this point a staff physician in TTH where adult thalassemia patients were being treated.
(ii) letter, Olivieri to McKay (HPB), 961113—requests HPB authorization further 90 day supply from Apotex; there is no mention of Dr. Koren in this letter—other than McKay and Olivieri, the only person named in this letter is N. Klein, a data manager who was keeping a record of EDR drug authorizations of patients under the care of Dr. Olivieri.
11. *Food and Drugs Act and Regulations*, section C.08.010.
12. G. Koren, “The Process of Ethics Review in Pediatric Research: The Toronto Model” in *Textbook of Ethics in Pediatric Research* (Malabar, Florida: Krieger Publishing Company, 1993) p. 197–220, at 198.
13. E-mail, Aberman to Durie *et al.*, 980830.
14. Letter, Koren to Becker.
15. Letter, Koren to Becker, 980415; and Naimark Report, p. 99.
16. Quotation from Naimark Report, p. 99.
17. E-mail from HSC Research Accounting to Olivieri, 970717; and year-end statement, 970331 to MRC on Olivieri’s grant account.
18. Letter, Spino to Koren, 971023.
19. Contracts for LA-01 (1993) and LA-03 (1995), and HSC cumulative account statement for LA-01.
20. E-mails, Aberman to Goldbloom, 960605 and 960608; and handwritten note by

- O'Brodovich on 960822 recording discussion with Aberman.
21. Naimark Report, p. 106.
 22. Naimark Report, p. 106.
 23. Memo, R.A. Clements (Borden&Elliot) to A.M. Christian (HSC), 971028.
 24. Legal opinion by Soberman, given to CoI, 000321 -- see Appendix F.
 25. Naimark Report, p. 106.
 26. Agreement signed by Olivieri, Prichard (UT) and Strofolino (HSC), 990125, appended to the present report.
 27. Naimark Report, p. 146.
 28. Naimark Report, p. 105.

Notes to Section 5H: Expanded disclosure

1. Letter, Olivieri and Koren to Zlotkin, 960715.
2. Letter, Olivieri and Koren to Dougherty, 960715.
3. Memo, Moore to file, 960717.
4. Letters: Moore to O'Brodovich, 970227 and 980603.
5. Trial termination notices for LA-03 and LA-01, Olivieri and Freedman to REB, signed by Olivieri on 960720 and 960721, respectively and by Freedman on 960725 —received by REB 960801. The Naimark Report records only the LA-01 termination form, indexed as N 113 (not archived by Naimark in HSC library archive). It appears that the Naimark Review did not have access to the LA-03 termination notice. Both these records were in REB files from 960801 onward.
6. Letter, Christian to Glasenberg (Chief Financial Officer, Apotex), 960705 .
7. Letter, Spino to Moore, 960729.
8. E-mail, Aberman to Durie *et al.*, 980830.
9. Letter, Olivieri and Koren to Spino (Apotex) 960607. It should be noted that the copy that the CoI has is not signed by Dr. Koren.
10. The covering letter, Olivieri to Spino, 960619 is not available to us, but it is referred to in the follow-up letter, Olivieri to Spino, 960620.
11. Letter, Olivieri to Spino, 960619.
12. Apotex acknowledged having such responsibilities in correspondence, for instance the letter, Spino to Koren, 971023, second sentence therein.
13. Letter, Kay to Olivieri (copied to Spino, Apotex Inc., Jack Kay, Apotex Inc., Freedman, Hospital for Sick Children, and Colangelo, McCarthy Tetrault), 960624.
14. Letter, Kay to Olivieri, 960624.
15. Letter, Spino to Koren, 960418; also, letter from Spino to Piga (an LA-02 investigator), 960315, which conveys Olivieri's February 1996 report.
16. Letter, Spino to Zlotkin, 960502, page 2, 3rd paragraph.
17. Letter, Spino to Olivieri, 960214, top of page 3.
18. Report of the Apotex EAP, July 12--13, 1996; and response to this report by Olivieri and Brittenham, August 1996.
19. Letter, Lee (CMPA) to Olivieri, 960807 .
20. Letter, Spino to Klein (HPB), 960813; and letter, Kay (counsel for Apotex) to Colangelo (counsel for Dr. Olivieri), 960814.
21. Letter, Kay (counsel for Apotex) to Colangelo (counsel for Dr. Olivieri), 960814 .
22. Letter, Colangelo to Kay, 960819, where he indicated that the meeting with HPB representatives had in fact taken place.
23. Letter, Olivieri to Spino, 960823; and letter, Colangelo to Kay, 960819.
24. Letter, Spino to Klein (HPB), 960814.
25. Letter, Olivieri *et al.* to Provost Sedra and HSC Board, 980905.
26. E-mail, Aberman to Naimark, 981008.

27. Handwritten note-to-file by Moore, 960717.
28. Memo-to-file by Mason, 960719; and handwritten notes by O’Brodivich, 960718—both from meeting with Olivieri *et al.* on 960718.
29. Memo-to-file by Mason, 960719.
30. Handwritten notes by O’Brodivich from meeting with Olivieri *et al.* on 960718.
31. Letter, Tricta to Olivieri, 961126.
32. Letter, Spino to Olivieri, 961127; see also letter, Spino to Olivieri, 960822.
33. See Olivieri’s submission to the MAC, 991012, binder III, Tab 50.
34. See Olivieri’s submission to the MAC, 991012: brief, p. 29-30; and binder III, Tab 50.
35. Letter, Spino to Olivieri, 960812.
36. Memo, Mason (McCarthy Tetrault) to Gertner (same firm), 960719.
37. Memo, Mason (McCarthy Tetrault) to Gertner (same firm), 960719.
38. Letter, Colangelo to Kay, 960819.
39. Letter, Olivieri to Spino, 960819.
40. Letter, Spino to Olivieri, 960822.
41. Letter, Olivieri to Spino, 960823.
42. Letter, Kay to Colangelo, 960823.
43. See: Olivieri’s submission to MAC, 991012, binder III, tabs 53, 54, 55; and letter, Olivieri to Koren, 970404.
44. Interviews of Olivieri and of Mason by CoI; and letter, Colangelo to Kay, 960819
45. Abstracts, by F. Tricta, G. Koren et al submitted to and delivered at “6th International Conference on Thalassemia ...,” Malta, April 6-10, 1997—the deadline for submission of the abstracts was December 01, 1996.
46. Letter, Colangelo to Kay, 960819.
47. Letter, Spino to Olivieri, 961127, copied to Dean Abeman and Dr. Goldbloom.
48. Letter, Colangelo to Kay, 960819.
49. Abstract, N.F. Olivieri, “Long-term follow-up of body iron in patients with thalassemia major during therapy with the orally active iron-chelator deferiprone (L1),” submitted to ASH 980822; published in supplement to *Blood*, 88:310a (1996).
50. Abstract, N.F. Olivieri, “Randomized trial of deferiprone (L1) and deferoxamine (DFO) in thalassemia major,” submitted to ASH 980822; published in supplement to *Blood*, 88:651a (1996).
51. Transcript of part of Olivieri’s talk at ASH, December 1996.
52. Review article, N.F. Olivieri and G.M. Brittenham, “Iron-chelating therapy and thalassemia,” *Blood*, 89, 3 (Feb. 1, 1997), p. 739-761. Article submitted 960229 and accepted 961001.
53. Review article, N.F. Olivieri and G.M. Brittenham, “Iron-chelating therapy and thalassemia,” *Blood*, 89, 3 (Feb. 1, 1997), p. 753.

Notes to Section 5I: Ongoing legal warnings

1. Letter, Spino to Olivieri and Koren, 960524.
2. Letters: Kay (Apotex counsel) to Olivieri, 960624; Spino to Olivieri, 960812; Kay to Colangelo, 960814; Spino to Olivieri, 960822; Kay to Colangelo, 960823.
3. Letter, Spino to Olivieri, 960812.
4. Letter, Spino to Olivieri, 961127.
5. Letter, Kay to Colangelo, 960814.
6. Letter, Spino to Olivieri, 961107.
7. Letter, Brown (Apotex counsel) to Colangelo, 970211.
8. Letter, Brown (Apotex) counsel to Colangelo, 970211.
9. Letter, Brown (Apotex) counsel to Colangelo, 970211.
10. “Practitioner” is the term for the treating physician under the EDR program in the *Food*

and drugs Act and Regulations.

11. Letters re: Washington abstract: Colangelo to Brown, 970217, and Brown to Colangelo, 970218—neither of these was deposited in HSC archives by Naimark, but the content summaries in the Naimark Report's index of documents confirm that the abstract was withdrawn. See also under arch tab 70, memo from journal staff to O'Brodovich, dated 981117, replying to his inquiry confirming abstract withdrawn.
The letter, Spino to Brittenham, 970306, confirms that Olivieri withdrew the abstracts she had submitted to the April 1997 Malta and the April 1997 Washington conference.
Olivieri reported to this inquiry that she withdrew as an author of the Brugge abstract, and that it was submitted and presented by Brittenham alone. This is confirmed by examination of the letters: Spino to Brittenham, 970306; and Olivieri to Colangelo, 970304 (Olivieri refers to "Brussels" meaning Brugge).
12. See letters: Spino to Brittenham, 970306 and 970307 – the quotation from Brittenham's Letter to Spino of 970306 appears in Spino's reply to Brittenham of 970307. Brittenham's letter was not available to us.
13. Letter, Brown to Colangelo, 970403.
14. Letter, Brown to Colangelo, 970508.
15. Letter, Kay to Colangelo, 970526 .
16. "Statement of Defence and Counterclaim" by Apotex, 000619, par. 123.
17. Letter, Spino to Naimark, 981124.
18. See CBS News *60 Minutes* Transcript dated 10 December 1999—attached to Sherman "Statement of Defence and Counterclaim" of June 19, 2000.
19. "Statement of Defence and Counterclaim" by Sherman/Apotex, 000619.
20. "Statement of Defence and Counterclaim" by Sherman/Apotex, 000619, 4th page of Schedule A.

Notes to Section 5J: Trial close-outs and another stoppage in supply of L1

1. LA-01 protocol, as modified 951005, section 5.4.13.
2. See for example, the letters: Woolcock to Olivieri and Koren, 960808; Spino to Olivieri and Koren, 960812; Olivieri to Spino, 960823. See also the letter, Olivieri to LaPlante (Apotex), copied to Koren and Aberman, 960913.
3. Brief, Olivieri to MAC, 991012, MAC binder I, p. 32.
4. Letter, Spino to Olivieri, 961115.
5. On July 15, 1996, Drs. Olivieri and Koren wrote to Dr. Zlotkin with a copy to his successor as REB Chair, Dr. Moore, that Apotex had terminated both clinical trials at the HSC and TTH and that the patients would be receiving L1 under the Emergency Drug Release provisions of Health Canada. Later that month, on the annual reporting forms, Drs. Olivieri and Freedman formally advised the REB that both LA-03 and LA-01 had been terminated (forms signed July 20, and 21, respectively, by Olivieri and both forms signed by Freedman July 25, and stamped as received by the REB on August 1, 1996).
6. See letter, Woolcock of Apotex to Olivieri, 960627, in which Woolcock made it clear that the drug release of L1 was under EDR (letter was captioned: Subject: Emergency Drug Release and it cites the *Food and Drug Act Regs.*).
7. Letter, Olivieri to Koren, 961028, copied to Aberman and N. Klein.
8. Letter, Spino to Goldbloom, 96103. This letter was not available to this inquiry. The summary of it in the index to the Naimark Report says, "requesting meeting with Goldblom [sic], Koren, freedman [sic] and Aberman re: supplying L1."
9. Memo to file by Goldbloom, 961114, re: meeting on 961113.
10. Letter, Klein to Koren, copied to Aberman, 961122.
11. Letter, Koren to Spino, copied to Freedman, 961125.

12. Letter, Olivieri to Spino, 961202. This letter was not available to this committee of inquiry, but the summary in the Naimark index says, “re: provision of L1 under EDR.”
13. Letter, Olivieri to parent of a patient, copied to Goldbloom, O’Brodivich and Aberman.
14. Letter, Spino to Olivieri, 961127 (letter issues another legal warning to Olivieri and outlines Apotex’s unresolved disagreement with Brittenham over access to audited source data).
15. Letters: Olivieri to Spino, 961115, with enclosed data; and reply by Spino, 961122.
16. Memo to file by Goldbloom, 961114.

Notes to Section 5K: Identification of the second risk

1. Article, P. Carthew *et al.*, *Biometals*, 7 (1994), pp. 267–271.
2. Transcript of Olivieri’s talk during ASH meeting, December 6–10, 1996.
3. Abstract, A.V. Hoffbrand, B. Wonke *et al.*, published in Supplement to *Blood*, December 1996, abstract# 2592.
4. Transcript of Olivieri’s talk during ASH meeting, December 6–10, 1996.
5. Letter, Olivieri *et al.* to Sedra and HSC Board members, 980905; and testimony of Olivieri. See also letter, Spino to Naimark, 981124, p. 2.
6. Memo, O’Brodivich to Naimark, 980924, page II-3; purported letter, Koren to Olivieri, purportedly dated 961218, reproduced at page 41 of the Naimark Report; letter, Koren to Roy (MAC) 981218.
7. Letter, Mason (CMPA) to Kay (Apotex counsel), 970114 -- in reply to letter, Kay to Colangelo (CMPA), 981218, regarding the question raised by Dr. Olivieri at ASH on fibrosis.
8. Statement by Cameron (liver pathologist), 990318.
9. Statement by Cameron (liver pathologist), 990318.
10. Public statement by Olivieri, 981210, titled “To all my patients ...;” and statement by Cameron, 990918.
11. Statement by Cameron, 990918.
12. Statement by Cameron, 990918.
13. Article, P. Carthew *et al.*, *Biometals*, 7 (1994), pp. 267–271.
14. Report by Olivieri, Brittenham and Cameron to FDA, HPB and other regulators, mis-dated 970122, not signed by Cameron until 970201, not sent to regulators until 970224.
15. Report by Olivieri, Brittenham and Cameron to FDA, HPB and other regulators, mis-dated 970122, not signed by Cameron until 970201, not sent to regulators until 970224.
16. Report by Olivieri, Brittenham and Cameron to FDA, HPB and other regulators, mis-dated 970122, not signed by Cameron until 970201, not sent to regulators until 970224, page 4.
17. Report by Olivieri, Brittenham and Cameron to FDA, HPB and other regulators, mis-dated 970122, not signed by Cameron until 970201, not sent to regulators until 970224, page 3.
18. Interview of Mason by committee of inquiry, 001216.
19. Public statement by Olivieri, 981210.
20. Public statement by Olivieri, 981210.
21. Memo, Olivieri to O’Brodivich and Freedman, 970306, par. (d).
22. Statement by Cameron, 990318; letter, Olivieri *et al.* to Sedra and HSC Board, 980905.
23. Letter, Olivieri to O’Brodivich, 970220 and memo, Olivieri to O’ Brodivich and Freedman, 970306.
24. Letters: Olivieri to Dr. O’Brodivich and Dr. Moore, 970220; and memo, Olivieri to Dr. O’Brodivich and Dr. Freedman, 970306. See also the review article, N.F. Olivieri and G.M. Brittenham, *Blood*, 89, 3 (February 1, 1997), pp. 739–761 (submitted 960229, accepted 961001).
25. Letters: Olivieri to Dr. O’Brodivich and Dr. Moore, 970220; and memo, Olivieri to Dr.

- O'Brodovich and Dr. Freedman, 970306.
26. Letters: Olivieri to O'Brodovich and to Moore, 970220.
 27. Letter, Olivieri to O'Brodovich, 970220; and memo, Hales (pharmacy) to O'Brodovich, 981026, confirming no prescriptions filled after 970218.
 28. Memo, Olivieri to O'Brodovich and Freedman, 970306; and Olivieri's information sheet for patients for the meeting held 970306.
 29. Letter, Colangelo to Kay, 970204.
 30. Letter, Kay to Colangelo, 970207.
 31. Letter, Brown to Colangelo, 970211.
 32. Letter, Colangelo to Olivieri and Koren, 970205.
 33. Memo, Koren to Olivieri, 970815; letters: Koren to O'Brodovich, 971103 and 971126; letter, Koren to Buchwald, 980511; and letter, Koren to Becker, 980415. These documents refer to activities in the period after the trials were terminated—the first three refer primarily to the former LA-01 patient cohort, the last two primarily to the former LA-03 patient cohort.
 34. Brief, Olivieri to MAC, 991012, p. 48.
 35. Naimark Report, p. 42.
 36. Letter, Brown to Colangelo, 970211.
 37. Dr. Koren acknowledged receipt of the copy of the report on the new risk sent to him by Dr. Olivieri through their joint counsel "in early February 1997" (Humphrey Report, p. 195). He also submitted a letter bearing the date "Feb 8, 1997" to the Naimark Review that he alleged he wrote on that date, saying he had received Dr. Olivieri's report.
 38. Memo, O'Brodovich to Naimark, 980924, page II-5 and page III-2, entry for February 19, 1997.
 39. Testimony by Olivieri to C of I. See also: memo, O'Brodovich to Naimark, 980924, pages II-5, III-2, III-3; and minutes of meeting on 970219 involving O'Brodovich, Freedman and Olivieri—minutes taken by Walker. Olivieri noted in a memo to O'Brodovich on 970305 that Walker's minutes were inaccurate in specific respects..
 40. Minutes of meeting involving O'Brodovich, Freedman and Olivieri, 970219—minutes taken by Walker.
 41. Memo, O'Brodovich to Naimark, 980924, page II-5.
 42. Letter, Moore to Olivieri, 970220.
 43. a) letters, Olivieri and Koren to: Zlotkin, copied to Moore, 960715; and to Dougherty, copied to Zlotkin, 960715.
b) termination notices, Olivieri and Freedman to REB, signed 970720, 21, 25 and stamped as received by REB on 960801.
 44. *Terms of Reference*, HSC REB, as revised 981211.
 45. Letters, Olivieri to Moore and to O'Brodovich, 970220.
 46. Letter, Moore to Olivieri, 970224.
 47. Memo, O'Brodovich to Naimark, 980924, page III-3.
 48. Letter, O'Brodovich to Moore, 970226.
 49. Letter, Moore to O'Brodovich, 970227.
 50. Note to file by Moore, 960717.
 51. Termination notices for each of LA-01 and LA-03, Olivieri and Freedman to REB, signed by Olivieri 960720&21 and by Freedman 960725, and stamped as received by REB 960801.
 52. Letter, Moore to O'Brodovich, 980603.
 53. Summary of testimony by Moore to MAC ad hoc subcommittee, 990111.
 54. Letter, Moore to O'Brodovich, 980603.
 55. Memo, Colangelo to file, 970227.
 56. Humphrey Report, released 991220, p. 195.
 57. Letter, O'Brodovich to Baker, 970220.
 58. Memo, O'Brodovich to Naimark, 980924, page III-3, entry for February 28, "O'Brodovich who had stopped the use of L1 at Hospital for Sick Children" In his letter

to Dr. Baker on February 20, he listed the steps he had taken as of that date, and stopping use of L1 was not on this list, so this additional action must have been taken later, on or about February 28.

59. E-mail between O'Brodovich and Freedman, 970228.
60. Letters, O'Brodovich to Olivieri, 970228 and 970304.
61. Letter, Olivieri to O'Brodovich, 970227.
62. Letters, Moore to Olivieri, 970224 and 970430.
63. Memo, O'Brodovich to Naimark, 980924, page III-3, entry for February 24.
64. Letters, Colangelo to O'Brodovich, 970228 and 970303; memo, Olivieri to O'Brodovich, 970305; and memo, Olivieri to O'Brodovich and Freedman, 970306.
65. Letter, Carter to O'Brodovich, 970311 (referring to meeting of March and previous correspondence).
66. Memo, O'Brodovich to Naimark, 980924.
67. See: REB minutes for its meeting of 970214; and Dr. Olivieri's brief to the MAC, 991012, pages 46-49.
68. Minutes, REB, 970214.
69. Letter, Moore to Olivieri, 970224.
70. Memo, O'Brodovich to Naimark, 980924, page III-3.
71. Information sheet, "Summary for Patients and Parents," distributed at group information meeting by Dr. Olivieri on 970306.
72. Letter, Spino to Freedman and Baker, copied to O'Brodovich, 970306.
73. Letter, Baker to Spino, 970417.
74. Letter, Spino to Freedman and Baker, copied to O'Brodovich, 970306.
75. Letter, Spino to pathology directors of TTH and HSC, 970305.
76. Final written report by Callea, 970524.
77. Letter, Spino to O'Brodovich, 970423.
78. Letter, Spino to O'Brodovich, 970423.
79. Letters: Colangelo to Brown, 970507; and Brown to Colangelo, 970708.
80. Letters: Spino to Freedman and Goldbloom, 970619, and Spino to Aberman, 970619.
81. Letter, Olivieri to CMPA lawyers, 970515, conveying information from Netten's notes on May 8/97 meeting of Apotex with patients.
82. Letter, Kay to Colangelo, 970526.
83. Testimony of Olivieri, Dick and Nathan (all of whom attended the Cooley's Anemia Foundation symposium in June 1997) to CoI.
84. Article, N.F. Olivieri *et al.*, *New England Journal of Medicine*, 339, 7 (August 13, 1998), pp. 417-423.
85. Memo, O'Brodovich to Naimark, 980924.

Notes to Section 5L: Events at the Hospital

1. Letter, Dick to Buchwald, 971007 (not sent until 971127, due to intervening meetings with Buchwald), reviewing a discussion they had on 970609.
2. Letter, Dick to Buchwald, 971007 (not sent until 971127, due to intervening meetings with Buchwald), reviewing a discussion they had on 970609.
3. Interview of Durie with CoI, 991102; and notes by Durie from meeting of 970911, recorded in memo to Olivieri of 970929.
4. Letter, Gallie to Buchwald and Strofolino, 980603.
5. Letter, Gallie to Buchwald and Strofolino, 980603.
6. Letter, Buchwald to Gallie, 980610.
7. Petition letter, signed by Durie, Dick and many others, 980626.
8. Letter, Buchwald to Gallie, 981207.
9. Petition letter, Durie and others to Buchwald, 980626.

10. Petition letter, Durie and others to Buchwald, 980626.
11. Letter, Zlotkin to Buchwald, 980630.
12. Letter, Corey to Buchwald, 980721.
13. Article in *Globe and Mail*, 980814.
14. Letter, Corey to Buchwald, 980721; and interview with Committee of Inquiry, 991103.
15. Letter, Saunders to Buchwald, 980723 – in this letter, Dr. Saunders stated that Ms. Anne-Marie Christian, the administrator responsible for reviewing contracts had approved his contract with Sangstat.
16. Letter, Blanchette, Koren and other division chiefs to Pitblado, 980821.
17. Notes by Dick of meeting with Buchwald, 971111.
18. There is extensive correspondence among Olivieri, various administrators, and others in March, April and May 1998 concerning Diav-Citrin's access to information on a patient, beginning with a letter from Olivieri to her on 980324. (March 24, 1998 is the date of the incident in question.)
19. Letter, Spino to Koren, 971023; and letter, Koren to O'Brodovich, 971103.
20. Letter, Olivieri to Becker, 980402
21. Letter, Koren to Olivieri, 980325.
22. Letter, Koren to Becker, 980415.
23. Letter, Moore to Buchwald, 980415.
24. Letter, Buchwald to Becker, 980420.
25. Letter, Olivieri to Becker, 980402.
26. letter, Koren to Becker, 980415.
27. Letter, Koren to Buchwald, 980507.
28. Letter, Sher to Keating, TTH, 970602, page 5, "I did perform a one-year consultancy for Apotex Inc. for which I was paid the sum of \$15,000. The purpose of this consultancy was as a medical advisor screening enrollment criteria for patients entering a project of L1 use in Italy"
29. Handwritten note to file by Koren, 980514, re: meeting with Spino and Tricta on 980513.
30. Article, O. Diav-Citrin, G. Atanackovic and G. Koren, *Therapeutic Drug Monitoring*, 21 (1999), pp. 74–81.
31. Article, *Toronto Star*, 980814.
32. Lawsuit by Koren against Gallie, the *Star* and the *Globe and Mail*, filed 981117.
33. Information from Hudgins (UTFA) to committee of inquiry, 010314.
34. Memo, Lister (HSC Foundation) to Naimark, 981030.
35. Memo, Lister (HSC Foundation) to Naimark, 981030.
36. Letter, Lister to Dellandrea, 980625.
37. Apotex submissions to regulators, dated 980126 and 980130.
38. Naimark Report p. 98.
39. Letter, Spino to Strofino, 980831.
40. E-mail memo, HSC Executive to all medical and scientific staff, 980901.
41. E-mail, Grinstein to many, 981012, with the September 1, 1998 statement by the HSC Executive attached.
42. Letter, Olivieri *et al.* to Sedra and HSC Board, 980905, pp. 11–12.

Notes to Section 5M: Removal of Dr. Olivieri as Director

1. Letter, Weatherall to Prichard, 990108.
2. Letters, Olivieri to Freedman, 950220 and 960513.
3. Letter, Olivieri to Freedman, 960215.
4. Memo, Goldbloom to file, 960409.
5. Letter, Olivieri to Freedman, 960508.
6. Letter, Freedman to Olivieri, 960510.

7. Letter, Vichinsky to Shelton and Searles, 961025 .
8. Letter, Olivieri to Freedman, 960508 (and attached letter, Olivieri to Freedman, 950220)
9. Article, *The Medical Post*, 971028.
10. Letter, Olivieri to Freedman, 960513.
11. Letter, Olivieri to Freedman, 960513—emphasis in original.
12. Letter, Goldbloom to Olivieri, 961018.
13. Memorandum, Dr. John Evans to Committee of Inquiry, 991125—see section 3.C.
14. E-mail, Olivieri to O’Brodivich, 961020.
15. Letter, Searles and Shelton to O’Brodivich, 961213.
16. Letter, Searles and Shelton to O’Brodivich, Dr. Goldbloom and Ms. Booth, 970211.
17. Letter, O’Brodivich to Olivieri and Goldbloom, 970217.
18. Draft letter, O’Brodivich to Searles, 970213, with Olivieri and Goldbloom listed as co-signatories; letter, Olivieri to O’Brodivich, 970219; and letter, O’Brodivich to Searles, 970225, essentially the draft of 970213, but co-signed by Goldbloom and Booth.
19. Letter, O’Brodivich *et al* to Searles, 970225.
20. Letter, O’Brodivich *et al.* to Searles, 970225.
21. “Facts Sheet” distributed by the Sickle Cell Disease Association, undated.
22. Letter, Shelton to HSC Board, 970409.
23. Letter, Olivieri to Freedman, 970824.
24. Letter, Olivieri to Blanchette and Gallie, 980415.
25. E-mail, Olivieri to Aberman, 980818.
26. Letter, Ruby (counsel for Olivieri) to Carter (counsel for HSC), 981113.
27. Letters, Olivieri to Blanchette, 980711, 980805, 980808, 980814, 981028, 981030 and 981104.
28. MRC General Guidelines for All Salary Supported Investigators (1997–1998), par. 298.
29. Article, *National Post*, 981211, referring to HSC press release of 981209.
30. Article, *The Sunday Sun*, 981213.
31. Minutes, Combined Chiefs Meeting, 981216.
32. Letter, Sedra to Graham, 990112.
33. Letter, Blanchette and O’Brodivich to Olivieri, 990106.
34. Letter, Sedra to Graham, 990112; minutes, Academic Board, 990121.
35. Letter, O’Brodivich and Buchwald to Olivieri, 990106.
36. Letter, Buchwald and Wedge (Surgeon-in-chief) to Gallie, 990106; reference to identical letters to Chan and Durie appears in minutes of the Acad. Bd., 990121.
37. Minutes, Academic Board, 990121.
38. Letter, O’Brodivich and Blanchette to Olivieri, 990106.
39. See, for instance: letter, Olivieri to Freedman, 950220; and letter, Shelton to Board of Trustees, 970409.
40. Agreement, signed by Prichard, Strofolino and Olivieri, 990125.
41. Letter, Weatherall to Prichard, 990108.
42. Letter, O’Brodivich and Buchwald to Olivieri, 990106.
43. Naimark report, p. 105.

Notes to Section 5N: Events at the University of Toronto

1. Twelve-point statement by the University, issued 981203, web-posted 981215, point 2.
2. Statement by Prichard, 981209.
3. Minutes, Governing Council, 981105, p. 10.
4. Twelve-point statement by the University, issued 981203, web-posted 981215, point 3.
5. Article, *The Bulletin* (UT), 981214.
6. Minutes, Governing council, 981105.

7. Letter, Prichard and Strofolino to Koren, 000411.
8. E-mail, Aberman to Naimark, 981008—this records that Dean Aberman and Mr. Kay “met at the Prince Hotel coffee shop.”
9. E-mail, Aberman to Naimark, 981008.
10. Letter, Spino to Olivieri, 960812, copied to Aberman, Kay and Koren; letter, Spino to Olivieri, 960822, copied to Aberman, Goldbloom and Koren; letter, Spino to Olivieri, 961107, copied to Aberman and Goldbloom; letter, Spino to Olivieri, 961127, copied to Aberman, Goldbloom and Koren.
11. E-mail, Aberman to Naimark, 981008.
12. Handwritten note by O’Brodivich on copy of letter, Spino to Olivieri, 960822, copied to Aberman, Koren *et al.*
13. E-mail, Aberman to Naimark, 981008 .
14. Letter, Munroe-Blum to Olivieri, 970924.
15. Letter, Olivieri to Sedra, 971027.
16. Letters, Gooch to Olivieri, 971127 and 971202.
17. Letter, Olivieri to Munroe-Blum, 980801.
18. Letter, Olivieri to Munroe-Blum, 980801.
19. Letters between Olivieri and Munroe-Blum, 980801 and 980806.
20. Letter, Sedra to Olivieri, 980812.
21. E-mail, Olivieri to Aberman, 980818.
22. Letter, Aberman to Olivieri, 980820.
23. Letter, Olivieri and Koren to Haslam, 960525, copied to Aberman and others.
24. Letter, Weatherall to Aberman, 970721.
25. E-mail reply Aberman to Weatherall, 970801.
26. Testimony of Nathan to CoI, 991103 and notes to file by Dick on conversation with Nathan, 970922.
27. E-mail, Aberman to Goldbloom *et al.*, 980902.
28. E-mail, Phillips to Olivieri, 970702.
29. Letter, Phillips to Aberman *et al.*, 970922.
30. Reply letters to Phillips from Aberman, 981001, and O’Brodivich and Buchwald, 971003; letter, O’Brodivich and Buchwald to Lamont, 971003; response by Phillips, 971005.
31. See sections 5H, 5I, 5K and 5T.
32. See sections 5H, 5I, 5K and 5T.
33. Priority Review Submission to Health Canada by Apotex Research Inc., 970930.
34. (i) Abstract on LA-03 data submitted to April 5-10, 1997 conference in Malta on thalassemia, by F. Tricta, G. Sher, R Loebstein, G. Atanackovic, O. Diav-Citrin and G. Koren, “Long-term chelation therapy with the orally active chelator deferiprone (L1) in patients with thalassemia major;” and
(ii) Abstract on LA-01 data for conference in Malta , April 5-10, 1997, on LA-01 data, by F. Tricta, G. Dougherty, O. Diav-Citrin, R. Lobstein, G. Atanackovic and G. Koren, “Randomized trial of deferiprone (L1) and deferoxamine (DFO) in thalassemia major.”
35. Abstract on LA-03 data submitted to April 1997 conference in Malta on thalassemia, by F. Tricta, G. Sher, R Loebstein, G. Atanackovic, O. Diav-Citrin and G. Koren, “Long-term chelation therapy with ... deferiprone”
36. (a) Report of the Friedland committee, 970909, page 4;
(b) Letters, Sher to Haslam, 951025 and Sher to Olivieri, 940624.
37. Letter, Sher to Haslam, 951025.
38. Letter, Olivieri to Phillipson, 960626.
39. Letter, Sher to Keating, 970602.
40. Testimony of Olivieri to CoI, 000607.
41. Report of the Friedland committee, 970909, p. 5; see also: letter Olivieri to Phillipson, 960626; information of Olivieri to CoI, 000607.

42. Letter, Spino to Felice (an organizer of the April 1997 Malta conference), 970613.
43. Dr. Olivieri learned of the existence of these abstracts in mid-February 1997, when she saw a copy of the conference program, but she was not provided with copies of the abstracts until shortly before the conference began. The CMPA legal counsel (who were still jointly representing her and Dr. Koren) obtained copies from Apotex, after first trying unsuccessfully to obtain copies from Dr. Koren. See letters: Olivieri to Colangelo and Mason (CMPA), 970213, 970214 and 970304; and Olivieri to Koren, 970404.
44. Letters, Olivieri to Sher, 970425 and 970512.
45. *Framework for Ethical Conduct of Research and Guidelines to Address Research Misconduct*, Faculty of Medicine, UT, revised 1996.
46. Letters: Olivieri to Sher, 970512; Olivieri to Keating, 970523; and Olivieri to Phillipson, 970626.
47. Letter, Sher to Keating, 970602.
48. LA-03 contract, signed by Spino on 951002, and by Koren on 951010 and Olivieri on 951012.
49. *Framework for Ethical Conduct of Research and Guidelines to Address Research Misconduct*, UT.
50. Letter and attachment, Phillipson to Yip, 970704.
51. Report of the Friedland committee, 970909, p. 6.
52. Report of the Friedland committee, 970909, p. 5.
53. Report of the Friedland committee, 970909, p. 6.
54. Report of the Friedland committee, 970909, p. 4.
55. Report of the Friedland committee, 970909, p. 7.
56. Report of the Friedland committee, 970909, p. 5.
57. Report of the Friedland committee, 970909, p. 2.
58. Report of the Friedland committee, 970909, p. 5.
59. (a) Drafts of abstracts re: efficacy of L1 in LA-03 trial cohort, with handwritten edits by Koren, July-August 1996 (abstract intended for ASH, Dec. 1996 meeting);
(b) Interview with Olivieri, November 1999;
(c) Letter, Olivieri to Koren, 970404;
(d) Letter, Colangelo to Kay, 960819.
60. *Framework for Ethical Conduct of Research and Guidelines to Address Research Misconduct*, UT (see Faculty of Medicine Calendar section, , pp. 66-67).
61. Letter, Aberman to Sher, 970911, copied to eleven others.
62. Letter, Aberman to Sher, 970911, copied to eleven others.
63. Article, O. Diav-Citrin, G. Atanackovic and G. Koren, *Therapeutic Drug Monitoring*, 21, 1 (1999), pp. 74-81.
64. Minutes, Governing Council, 990204.
65. *University of Toronto Publication Policy*, approved by the Governing Council, 750227.
66. Report number 90 of the Academic Board, 981008.
67. Letters, Ranalli to Prichard and Aberman, 970204; the available copy of Ranalli's letter to Prichard has a handwritten note by Prichard asking Aberman to "reply on my behalf"; reply by Aberman, 970209.
68. Letter and appendix, Hudgins to Naylor, 991117.
69. Dickens Report, April 1999, p. 18.
70. Statement by Dean Naylor in *Med.E.Mail*, and electronic newsletter of the Faculty of Medicine, 010326.
71. Article in *The Toronto Star*, 010327, p. A9.
72. Letter, Singer to committee of inquiry, 010125.
73. Statement by the University, 981203, point 5.
74. Naimark Report, p. 138.
75. Naimark Report, p. 146.

76. Report number 90 of the Academic Board, 981008.
77. Statement by UT, 981203.
78. Minutes of the Governing Council, 981217, p. 8.
79. Statement by UT, 981203.
80. Report by Dickens, titled, "Harmonization of Research Policies and Procedures Between the University of Toronto and its Affiliated Teaching Hospitals," April 1999.
81. Appendix A, dated 990218 (terms of reference) to Dickens Report, April 1999.
82. Public statements: by the University of Toronto, issued 981203, and by President Prichard, 981209, posted on the UT website; and article in *UT Bulletin*, 981214.
83. Letter, Hudgins to Cook, 990910.
84. Interview of Dickens by CoI, 991104.
85. Statement by Naylor, 010326, in *Med.E.Mail*, 9, 26 (March 26, 2001), pp. 4-8.
86. Statement by Naylor, 010326, in *Med.E.Mail*, 9, 26 (March 26, 2001), p. 6.
87. News stories in the *Globe & Mail* and in the *Star*, 010227—the grievance hearings in the University began on 010226; the Hospital filed its court action to block the summonses on 010223.

A decision on the Hospital's application was issued on 010709 by Nordheimer J. of the Ontario Superior Court of Justice who concluded: (i) the University's Grievance Review Panel had the authority under the *Arbitration Act, 1991* to issue summonses; (ii) it was premature at this stage of the particular grievance proceedings to enforce summonses issued to date.
88. Letter, Prichard and Strofolino to Koren, 000411, p. 5.
89. Letters: Spino to Hindmarsh (Dean of Pharmacy), 980924; and O'Brien (Graduate Chair of Pharmacy), 980413.
90. Testimony of Chan to CoI; letter, Graham to Sedra, 990121.
91. Letter, Sedra to Graham, 990112—describing discussion between Prichard and Strofolino.
92. Letter, Sedra to Graham, 990112.
93. Minutes, Academic Board, 990121.
94. Letters, Sedra to Graham, 990112, Aberman to Strofolino, 990113, Graham to Prichard, 990119.
95. Detailed record of discussion, meeting of 990120 at Intercontinental Hotel.
96. Minutes, Academic Board, 990121.
97. Letter, Graham to Prichard, 990121.
98. Letter, Graham to Porter, 990120.
99. Minutes, Academic Board, 990121, item 10, p. 10.
100. Dr. John Porter of University College, London and Dr. Alan Schechter of NIH, Bethesda submitted the report of their review of the scientific aspects of Dr. Olivieri's hemoglobinopathy program in the University, HSC and TTH to Professor Graham, President of CAUT, on February 9, 1999. The reviewers found that, "Dr. Olivieri's program of clinical research by any criteria is outstanding." They also stated that, "In order to initiate national and international trials, it is important that the unit is headed by an individual who has the respect of the international community and the authority to carry out the studies at the local level. Dr. Olivieri commands considerable respect in the international community as evidenced by her track record in publication and grant funding which is second to none in the field. If another person were to have been placed as head of the programme above her, this would undermine her credibility and authority and would likely prejudice important international collaborations."
101. Testimony by Weatherall to CoI, 991031.
102. Minutes, Academic Board, 990121, item 10, page 10.
103. Article, *UTFA Newsletter*, 990211, p. 3, column 1, meeting with CoI, 991103.
104. Interviews of Weatherall and Nathan with CoI, 991031 and 991103, respectively.
105. Letter, Weatherall and Nathan to Olivieri and Strofolino, 990125.
106. Agreement, signed by Prichard, Olivieri and Strofolino, 990125.

107. In January 1999, the number of hours physician assistants would be available for work in the HSC clinic was increased to the level it had been in the spring of 1998, prior to the reduction imposed by Dr. Blanchette in the summer of 1998. This fact is noted in the program review report of Drs. Porter and Schechter, dated 990208. As outlined in section 5M, the escalation during the second half of 1998 of the dispute over this reduction in clinical support culminated in the summary dismissal of Dr. Olivieri from her directorship in early January 1999.
108. Memo, Borden & Eliot to Christian (HSC), 971024, confirming telephoned advice, 970924.
109. brief by Olivieri to MAC, 991012, p. 53; and testimony of Drs. Olivieri, Chan and Gallie to CoI.
110. Testimony of Gallie to CoI, 991101.
111. Testimony of Gallie by CoI, 991101.
112. Humphrey Report, Chan's transcription, p. 137; and letter, Prichard and Strofolino to Koren, 000411.
113. Letter, Sedra to Graham and Love, 991209.
114. Humphrey report, Chan's transcription, p. 78.
115. Letter, Aird to Chan *et al.*, 991210.
116. E-mail memo, HSC Executive to many, 980901.
117. Allegations that Dr. Koren had submitted false information to the Naimark review were provided to the Hospital on 991012, through copies of Dr. Olivieri's response to the MAC.
118. Testimony by Chan to CoI, 000204: Chan reported to CoI that she and Durie had informed Toronto Police Detective Bone of the DNA identification of Koren, on or about December 9, and that Bone reported back to them that he had informed Koren that he had been identified in this way. See also *Globe & Mail*, 991221, "Dr. Gideon Koren ... said yesterday that he was recently visited by a Toronto police officer about the letters."
119. Articles: *Toronto Star*, 991221, *Globe & Mail*, 991221, *National Post*, 991221, and *Toronto Sun*, 991222.
120. Article, *Globe & Mail*, 991222.
121. E-mail, Dick to Naylor, 991221.
122. a) Prior to May 17, 1999, Dr. Koren was suspected of being the author of the anonymous letters, but not accused. On May 17, 1999 he was accused by Dr. Olivieri *et al.*, who had retained private detective and forensic experts who made the identification. The complaint and evidence were then presented to the Hospital and the University; additional forensic evidence was presented in June. (See section 5R(3).)
b) The common law on disciplinary action in employment matters is different from that of criminal law. See, for example, the column on employment law, *Globe & Mail*, 000814 by M. Mackillop, titled "Respond effectively to office poison pen letters," which summarizes the situation: "It is important to remember that the company does not have to prove that an employee is 'guilty beyond a reasonable doubt.' This is not a criminal investigation, and the onus on the company is to prove just cause on the 'balance of probabilities,' a standard of proof considerably less onerous than the standard applied in a criminal case."
123. Humphrey report, 991220.
124. Letter, Prichard and Strofolino to Koren, 000411.
125. Letter, Prichard and Strofolino to Koren, 000411.
126. Letter, Prichard and Strofolino to Koren, 000411.
127. Minutes, UT Governing Council, 981217.
128. Public statement by Prichard, 981209.
129. Naimark Report, pp. 106, 142.
130. Naimark Report, p. 42—this was Dr. Olivieri's abstract for the Biomedicine '97 conference. Apotex's request that she withdraw it was conveyed in a lawyer's letter containing a legal warning, Brown to Colangelo, 970211.
131. Public statement by Prichard, 981209.

132. Statement by the University, dated 981203, sent to Governing Council 981204, posted on website 981215 .
133. Report of the Academic Board, 981008.

Notes to Section 50: The Naimark Process & Report

1. Article, N.F. Olivieri *et al.*, “Long-Term Safety and Effectiveness of Iron-Chelation Therapy with Deferiprone for Thalassemia Major,” *New England Journal of Medicine*, 339, 7 (Aug. 13, 1998), pp. 417–423.
2. Toronto *Sun* and Toronto *Star*, Aug. 21, 1998.
3. Naimark Report, p. 1.
4. Public statement by Pitblado (HSC Board Chair), 980909.
5. The Naimark Report stated that the total Apotex funding to the University of Manitoba during 1989–1998 was \$789,840. Dr. Olivieri’s application to MRC for funding for the LA-01 trial under the university-industry program stated that the industrial co-sponsor was Apotex subsidiary Rh Pharmaceuticals Inc., 104 Chancellor Matheson Road, University of Manitoba Campus, Winnipeg, Manitoba, R3J 2N2.
6. Letters by Polanyi, Thompson, Hamilton, Nathan & Weatherall to Pitblado *et al.*, 981005 and 981006.
7. MSSA minutes, 981001.
8. Letter faxed by Naimark to Baird, 980929—an unsigned draft, on Naimark’s letterhead with his fax number printed on the top of the page by the fax machine.
9. Letter, Baird to Naimark, 980929.
10. Letter, Baird to Thompson (CoI), 990816, summarizing correspondence and notes of telephone discussions between Baird and Naimark, Sept. 27–Oct 7, 1998.
11. Letter, Naimark to Baird, 981007.
12. Letter, Baird to Naimark, 981007.
13. “Participation Agreement” signed by Drs. Gallie *et al.*, Oct. 19, 1998.
14. “Participation Agreement” signed by Drs. Gallie *et al.*, Oct. 19, 1998 and covering letter, Orved (CMPA counsel) to Carter (HSC counsel), Oct. 19.
15. This commitment was not written into the “Participation Agreement,” but was a verbal undertaking, and was noted by HSC President Strofolino in his e-mail to all staff, 981022 (see following endnote): “There has been an agreement that there will be no further discussion through the media and no further promotion of debate informally among colleagues by either the Hospital or affected staff.”
16. Memo, Strofolino to all staff, distributed by e-mail from his assistant, Capizzano, Oct. 22, 1998, 16:18 hours.
17. E-mails of Grinstein, 981012 and Buchwald, 981019.
18. These anonymous letters were written and sent by Dr. Koren.
19. announcements by Pitblado and by Doctors for Research Integrity (a group supporting Dr. Olivieri), 981104.
20. Naimark Report, p. 3.
21. Article in *This Week* (HSC publication), 981210; also, an article in *Toronto Star*, Dec. 10, 1998 gives list of key dates.
22. Naimark Report, p. 2.
23. Naimark Report, p. 129.
24. Naimark Report, p. 129.
25. Letter, Aird to Olivieri *et al.*, 991230.
26. Letter, Aird to Olivieri *et al.*, 991230; see also: open letter, HSC Board to HSC community, e-mailed by Dr. O’Brodivich, January 2000, hard copy in *This Week* (HSC newsletter), Jan. 13, 2000.
27. Humphrey Report, pp. 199–200 (Chan’s transcription, pp. 105–6)
28. Humphrey Report, pp. 199–200 (Chan’s transcription, pp. 135, 137).

29. Humphrey Report, (Chan's transcription, pp. 105–8, 118–120, 134).
30. Humphrey Report, p. 227 (Chan's transcription, p. 118)
31. Compare Naimark report, complete "reference list of documentation" with HSC archives catalogue of Naimark documents deposited there.
32. Letter, Spino to Naimark, 981124, referred to at p. 101 of Naimark Report.
33. Naimark report, p. 42, provides information from letters: (i) O'Brodovich to Naimark, 981125; and (ii) 981202.
34. Letter, O'Brodovich to Colangelo, 970303.
35. Memo, Koren to Buchwald, 980514.
36. Letters: Koren to Olivieri, 970815; Koren to O'Brodovich, 971103 and 971126. The memo, Koren to Buchwald, 980514, also contradicts the letters reproduced on page 41 of the Naimark Report.
37. The letters Dr. Koren alleged he had written on the dates specified in them are: Koren to Olivieri, 961218 and 970208.
38. Letter, Spino to Koren, 960418.
39. Letters: Kay to Colangelo, 961218, and Mason to Kay, 970114.
40. Naimark Report, p. 89.
41. Memo entitled "O'Brodovich submission to Dr. Naimark," and dated 980924.
42. Humphrey Report, p. 203 (Chan's transcription, p. 107).
43. Contract for LA-03, signed by Drs. Spino (951002), Koren (951010) and Olivieri (951012)
44. Trial termination notification forms for LA-03 and LA-01, signed by Olivieri and Freedman in July 1996 and stamped as received by REB on August 1, 1996.
45. Letter, Spino to Brittenham, 951003.
46. Letter, Spino to Olivieri, 960508.
47. Full report of the EAP.
48. Letter, Corey to Buchwald, 980721.
49. Book, G. Koren, ed., *Textbook of Ethics in Pediatric Research*, 1993 [get bibliogr. details], chapter 17, written by G. Koren, "The Process of Ethics Review in Pediatrics Research: the Toronto Model."
50. Letter, Spino to Olivieri, 960812.
51. Letter, Spino to A. Klein (of HPB), 960813.
52. Letter, Colangelo to Koren and Olivieri.
53. Letter, Brown to Colangelo, 970508.
54. Letter, Saunders to Buchwald, 980723.
55. Letter, Olivieri *et al.* to Sedra *et al.*, 980905.
56. i) Letters: Spino to A. Klein (Health Canada), 970128; and Woolcock to M. Carmen (Health Canada), 970225;
ii) Documents re: licencing applications: Priority Review Submission, Canada, 970930; Canada, prepared by Apotex Research, 980126, entitled, "Clinical Study Report LA-01—Comparative study of Exferrum and DFO; and Australia, prepared by Apotex Research, 980130, entitled, "Comprehensive Summary—Exferrum." Exferrum is an Apotex term for its drug L1. DFO is deferoxamine, the standard iron-chelation drug..
57. Letter, Olivieri to Koren, 961028.
58. MRC application file of Olivieri, re: L1 trials (see section 5A).
59. Letter, Spino to Moore.
60. Report of the Apotex EAP, dated 960712–960713.
61. Book, G. Koren, ed., *Textbook of Ethics in Pediatric Research*, chapter 17, p. 198, written by G. Koren.
62. Letter, Kay to Colangelo, 960814.
63. Naimark Report, p. 37.
64. Naimark Report, pp. 42, 134.
65. Letter, Olivieri to Colangelo and Mason, 970515, summarizing notes taken by social

worker K. Netten at the May 8 meeting where Drs. Spino and Tricta of Apotex spoke with Dr. Olivieri's patients.

66. Statement by Pitblado (HSC Board Chair), 980909.
67. "Open letter," HSC Board to employees, *This Week*, 000113.
68. Article by HSC Board Chair Alexander Aird in the *Globe and Mail*, 991231.
69. Resolution by HSC Board of Trustees, 981209, reported on in *National Post*, 981211; and "Statement of Defence and Counterclaim" by Apotex filed in Ontario Superior Court, 000619.
70. Statement by Prichard, 981209, UT website; and article in *The Bulletin*, UT, 981214.
71. Naimark Report, p. 21.
72. Naimark Report, p. 25.
73. Naimark Report, p. 103.
74. Naimark Report, pp. 118–126.
75. Draft report of the HSC Research Policy Review Task Force, 990712; and report on "Harmonization of Research Policies and Procedures ..." by Professor Dickens, April 1999.
76. Letters and attached report: Colangelo to Kay (Apotex's counsel), 970204, and to Koren, 970205.
77. Humphrey Report, p. 195 (Chan's transcription, p. 103).
78. "Letter," Koren to Olivieri, 961218.
79. Letter, O'Brodovich to Colangelo, 970303—copied to Koren and Olivieri.
80. Memo, O'Brodovich to Naimark, 980924, p. III-4—the memo misdates the Moore letter as June 3, 1997, instead of its actual date of June 3, 1998.
81. Naimark Report, pp. 30, 35 (in subsection heading and in text below it), and 99.
82. Naimark Report, page 30.
83. E-mail, Aberman to Durie *et al.*, 980830, N445 (arch 39)—quoted at page 33 of Naimark Report.
84. Naimark Report, pp. 35 and 99.
85. Naimark Report, pp. 21 and 146.
86. Front page of LA-02 protocol, 950721.
87. Letter, Olivieri and Koren to Zlotkin, copied to Moore, 960715.
88. Naimark Report, p. 35.
89. Letters, Koren to: Olivieri, 970815; O'Brodovich, 971103 and 971126; Becker, 980415; and Buchwald, 980514.
90. Letter, Christian to Glasenberg (CFO, Apotex), 960705.
91. Naimark Report, p. 99 and 143—apparently relying on two letters by Koren: to Becker, 980415; and to Buchwald, 980507.
92. Note to file by Koren, 980514; submitted article by Koren and two Apotex-funded fellows, received by journal August 12, 1998; and editor's letter of acceptance—the article was published in *Therapeutic Drug Monitoring*, 21, 1 (1999), pp. 74–81 (see section 5R).
93. Letter, Koren to Pitblado, 980820.
94. Naimark Report, p. 99.
95. Naimark Report, p. 41.
96. Letter, Olivieri to Koren, 961028, copied to Aberman and N. Klein.
97. University of Toronto Publication Policy dated 1995. We have seen no evidence that the Hospital for Sick Children had any publication policy in contract research, other than the University's policy, at the time the LA-01 contract was signed. The draft report of the HSC Research Policy Review Task Force, dated 990712, recommended policy development in this area (at pages 53–54).
98. Naimark Report, pp. 21 and 146.
99. Naimark Report, pp. 23–24.
100. Memo, Spino to other Apotex staff, 940625, page 3.
101. Naimark Report, p. 23.

102. Naimark Report, p. 106.
103. Naimark Report, p. 146.
104. Letter, Aird and Strofolino to Olivieri, 000117; and article in *The Bulletin* of the UT, 981214. Mr. Aird and Mr. Strofolino wrote, “One of the lessons learned [from the Naimark Review] was that it would have been appropriate for the Hospital to offer you more *visible* support in your dispute with Apotex. ... we agree that in retrospect the Hospital should have offered you more *visible* support when Apotex ... threaten[ed] legal action. We apologize for not doing so.” (emphasis added) It is reasonable to interpret this as meaning that HSC support was provided but was not sufficiently visible. However, the problem was that the support was not effective, regardless of its degree of visibility.
105. E-mail memo, HSC Executive to many, 980901; and e-mail, Aberman to Weatherall, 970731.
106. Naimark Report, p. 27, footnote.
107. Naimark Report, p. 145.
108. Naimark Report, p. 138.
109. Naimark Report, p. 106.
110. Naimark Report, pp. 105–6.
111. Naimark Report, p. 106.
112. Naimark Report, p. 138.
113. Naimark Report, p. 110.
114. Naimark Report, pp. 44, 45.
115. Purported letter, Koren to Olivieri, purportedly dated “December 18, 1996,” reproduced at page 41 of the Naimark Report. See also letter, Lishner to MAC, 981214.
116. Letter, O’Brodivich to Naimark, 981125.
117. Naimark Report, p. 89.
118. Naimark Report, p. 101.
119. Letter, O’Brodivich to Naimark, 981125—the letter refers to “the recent conference call” involving the two of them and others.
120. Letter, Spino to Naimark, 981124.
121. Letter, O’Brodivich to Naimark, 981125.
122. Naimark Report, p. 88.
123. Memo, Olivieri to O’Brodivich and Freedman, 970306, paragraph (d).
124. Memo, O’Brodivich to Naimark, 980924.
125. Naimark Report, p. 135; see also memo, O’Brodivich to Naimark, 980924.
126. “Letter,” Koren to Olivieri, allegedly written and sent on 970208—reproduced in full at page 41 of the Naimark Report.
127. See for instance the memo, O’Brodivich to Naimark, 980924 and the letter, Spino to Naimark, 981124.
128. Letter, Spino to O’Brodivich, 980522.
129. a) G. Koren, *Textbook of Ethics in Pediatric Research*, Krieger (1993), Ch. 17;
b) Letter, Moore to Buchwald, 980415; c) REB minutes, 980417.
130. Memo, O’Brodivich to Naimark, 980924.
131. For instance, the letters: Spino to Olivieri and Koren, 960524; and Spino to Strofolino, 980831, page 2..
132. Letter, Kay to Colangelo, 961218.
133. Letter, Kay to Colangelo, 961218 and reply, Mason to Kay, 970114.
134. Letter, Kay to Colangelo, 970207.
135. Letter, Brown to Colangelo, 970211.
136. Naimark Report, p. 42.
137. Letter, Spino to Freedman and Baker, 970306.
138. LA-02 trial protocol, dated 940630, and revised on 950721, p. 5.
139. See treatment monitoring regime proposed by Spino in an attachment to his letter, Spino

- to Freedman and Baker, 970306.
140. "Letters," Koren to Olivieri, purportedly written and sent on 961218 and 970208—reproduced at page 41 of the Report.
 141. Brief by Olivieri *et al.* to joint UT/HSC disciplinary panel, 000104; brief by Olivieri to MAC, 991012, p. 4.
 142. See letter, Prichard and Strofolino to Koren, 000411, for a summary of the allegation by Olivieri against Koren.
 143. Letter, Koren to O'Brodovich, 971103; another letter, Koren to O'Brodovich, 971126.
 144. Letter, Koren to Olivieri, 970815.
 145. Memo, Koren to Buchwald, 980514.
 146. *CV* of Koren.
 147. Letter, Koren to O'Brodovich, 971126—Dr. Koren wrote, "I served as a contact person between Dr. Olivieri and Apotex, to allow the Emergency release of the drug, as the two parties were not on speaking terms." Also, in other letters Dr. Koren confirmed he had no involvement with any aspect of the monitoring of patients who remained on L1 after May 1996 (see above and section 5P).
 148. Naimark Report, p. 134.
 149. Letter, Lishner to MAC, 981214.
 150. Letter, O'Brodovich to Colangelo, 970303.
 151. For instance: memo, O'Brodovich to Naimark, 980924; letter, O'Brodovich to Naimark, 981125; and letter, O'Brodovich to Naimark, 981028, enclosing letter from Naomi Klein to Koren dated 981028. See also, letter, O'Brodovich to Koren, 981126.
 152. (a) Memo, O'Brodovich to Naimark, 980924, page III-3, entry for Feb. 24/97;
(b) Letter, Carter to O'Brodovich, 970311 .
 153. Letter, O'Brodovich to Olivieri, 971021.
 154. Letter, O'Brodovich to Spino, 971117.
 155. Humphrey Report, p. 203 (Chan's transcription, pp. 107–8).
 156. Memo, Olivieri to O'Brodovich and Freedman, 970306, paragraph (d).
 157. Memo, Olivieri to O'Brodovich and Freedman, 970306, paragraph (c).
 158. Letter, Spino to Freedman and Baker, 970306, copied to O'Brodovich.
 159. Letter, Olivieri to O'Brodovich, 970220.
 160. Letter, Moore to O'Brodovich, 980603, copied to Olivieri—see section 5K for a discussion of the errors in this letter.
 161. Letter, Olivieri to O'Brodovich, 980608.
 162. Letter, O'Brodovich to Spino, 980610.
 163. a) Letters: Klein to Koren, 981028 and 981119; Klein to O'Brodovich, 981217.
b) Letters: O'Brodovich to Naimark, 981028, 981120 and 981129
c) Letters: O'Brodovich to Klein, 981126; O'Brodovich to Koren, 981126 and reply by Koren, same day.
d) Letter, Klein to O'Brodovich, 981217.
 164. Letter, O'Brodovich to Baker, 970220.
 165. Interview of Baker by CoI, 991215.
 166. Letter, Baker to Spino, 970417.
 167. Letter, O'Brodovich to Naimark, 991125, referring to Naimark's hypothesis.
 168. Naimark Report, pp. 100–101, with a footnote citing Spino's letter to Naimark, 981124.
 169. Letter, Spino to Naimark, 981124.
 170. Letter, Spino to Olivieri and Koren, 960524.
 171. Recorded telephone message, Spino to Olivieri, 960524. See section 5I for the complete message.
 172. Letter, Spino to Brittenham, 960617.
 173. Letter, Spino to Olivieri, 960214.
 174. Letter, Spino to Olivieri, 960216.

175. Correspondence: Spino to Zlotkin, 960315; Zlotkin to Spino, 960325; Spino to Koren, 960418.
176. Letter, Spino to Zlotkin, 960502.
177. Correspondence between Spino and Zlotkin, 960315, 960325, 960502 and 960510.
178. Letter, Spino to Olivieri and Koren, 960524.
179. Naimark Report, p. 101.
180. Letter, Colangelo to Kay, 970204.
181. Letter, Spino to Naimark, 981124.
182. Letter, Brown to Colangelo, 970211.
183. Letter, Spino to Olivieri and Koren, 960524.
184. Public statement by Olivieri, 981210, titled, "To my patients and to all those who care about the Hospital for Sick Children."
185. Public statement by Olivieri, 981210, titled, "To my patients and to all those who care about the Hospital for Sick Children."
186. Public statement by Olivieri, 981210, titled, "To my patients and to all those who care about the Hospital for Sick Children."
187. Public statement by Olivieri, 981210, titled, "To my patients and to all those who care about the Hospital for Sick Children."
188. Statement of Defence and Counter Claim by Sherman and Apotex, 000619, par. 77, 78.

Notes to Section 5P: The Medical Advisory Committee Proceedings

1. Resolution by the HSC Board of Trustees, 981209.
2. Letter, Roy (Chair, MAC *ad hoc* subcommittee) to Olivieri, 981223.
3. Letter, Roy (MAC) to Olivieri, 990216.
4. Letter, Symes to Stockwood, 990111.
5. Letter, Foerster (counsel for HSC Board) to Lace (counsel for Olivieri), 000310, conveying some documents from the documentary base of the Naimark Report that had not been deposited in HSC archives and so not previously available to Olivieri.
6. Letter, Shin (counsel for the MAC) to Lace (counsel for Olivieri), 000310, conveying some of the allegations and testimony (letters and summaries of interviews of witnesses) the MAC had received in the period December 1998–February 1999, none of which had previously been disclosed to Olivieri.
7. Response of Dr. Olivieri to the MAC, 991012, in three volumes .
8. Letter, Becker (MAC) to Olivieri, 000118, attaching report of *ad hoc* subcommittee (there is no date on the report itself); see also letter, Becker to Olivieri, 000126.
9. The letters from counsel Foerster and counsel Shin to counsel Lace, both dated 000310 (cited above), cite written requests by Dr. Olivieri or her counsel for disclosure dated: 000206 and 000229 (to Naimark); 000221, 000213, 000228 and 000302 (to MAC counsel or HSC counsel).
10. See endnotes 5 and 6 above (re: letters from Foerster and Shin, 000310 and their attachments).
11. The documentary information available to us (see letter, Shin to Lace, 000310) indicates that the first testimony to the MAC was Dr. Koren's letter, Koren to Roy (MAC), 981218 and the last was on 990209, when two witnesses were heard.
12. Letter, Koren to Roy (MAC), 981218; and letter, O'Brodo vich to Roy (MAC), 990204.
13. Letter, Becker to Olivieri, 000118, p. 2.
14. letter, Lace to Stockwood, 000330.
15. HSC press release, 000427, including MAC report dated "April 2000" (no specific day given) and open letter, Aird (Board Chair) to HSC employees.
16. Resolution by the HSC Board of Trustees, 981209.
17. Press release by HSC, 000427.

18. Report of the *ad hoc* subcommittee of the MAC, conveyed to Dr. Olivieri with a letter from Becker, 000118.
19. Letter, Roy to Olivieri, 981223.
20. Letter, Roy to Olivieri, 981223.
21. Letter, O’Brodivich to Roy, 990104.
22. Letter, Roy (MAC) to Olivieri, 990216; the questions are repeated in the Hospital’s press release dated 000427.
23. Letter, Symes to Stockwood, 990111.
24. Brief and 3 binders of supporting documents, Olivieri to MAC, 991012 .
25. Report of the *ad hoc* subcommittee of the MAC, conveyed to Dr. Olivieri with a letter from Becker, 000118.
26. Brief, Olivieri to MAC, 991012, in Vol. I, p. 34.
27. Brief, Olivieri to MAC, 991012, in Vol. I, pp. 46–49.
28. Report of the MAC *ad hoc* subcommittee to the MAC (undated), conveyed to Olivieri with letter by Becker dated 000118.
29. The complete list of six witnesses appears in the letter, Shin to Lace, 000310.
30. a) Letter, Berkovitch to Naimark, 980917;
b) E-mail, Berkovitch to Laxer (MAC), 000107, apparently written in reply to Laxer’s e-mail to Berkovitch.
31. E-mail exchange between Laxer and Berkovitch, 000107 and 000108. (i) Berkovitch wrote to Laxer (undated), “Dear Ron, I recieved [sic] you [sic] email. Since the letter [to Naimark] from september [sic] 1998 is located in my computer at home ... I asked Sefi to write my answers. ... It was written by me and only by me regarding liver biopsy [sic]. ... Sincerely yours Mati Berkovitch.” Laxer responded with a note on 000108, “Dear Mati, Thank you for the information. May I share this with my colleagues on the Medical Advisory Committee ...? The MAC has been asked to investigate for the Board whether some of Nancy’s practices were ‘research’ as opposed to ‘clinical care’. Many thanks, todah rabbah, Ron”
32. Letter, O’Brodivich to Roy (MAC), 990104.
33. Letter, Foerster to Lace, 000310.
34. Letters: O’Brodivich to Roy (MAC), 990104; Berkovitch to Naimark, 980917; and Atanackovic to Naimark, 981023.
35. E-mail, O’Brodivich to Olivieri, 960904. Dr. Nisbet-Brown was subsequently appointed director of the thalassemia clinic at Children’s Hospital, Boston, a Harvard teaching hospital.
36. a) Memo, O’Brodivich to Naimark, 980924, pp. II, 5 and III, 2;
b) E-mail between O’Brodivich and Freedman, 970226.
37. Humphrey Report, p. 203, referring to memo, O’Brodivich to Naimark, 980924.
38. Letters: Koren to Roy, 981218 and O’Brodivich to Roy, 990104; summaries of oral testimony by Koren and O’Brodivich to MAC, both on 990119.
39. Letters: Berkovitch to Haslam, 951120; and Berkovitch to Naimark, 980917 .
40. Article, M. Berkovitch, T. Bistrizter, S.D. Milone, K. Perlman, W. Kucharczyk, G. Koren and N.F. Olivieri, “Iron deposition in the anterior pituitary in homozygous beta-thalassemia: MRI evaluation and correlation with gonadal function,” *Journal of Pediatric Endocrinology & Metabolism*, 13, 2 (February 2000).
41. Testimony by Olivieri to CoI, 000521.
42. E-mail, Milone to Olivieri, 000626.
43. See Uniform Requirements for Manuscripts Submitted to Biomedical Journals, *New England Journal of Medicine*, Feb. 7, 1991, pp. 424–428.
44. Letters: Berkovitch to Naimark, 980917; Atanackovic to Naimark, 981023.
45. Letter, O’Brodivich to Roy, 990104.
46. See section 5.3 “Inclusion and exclusion criteria” of the LA-01 protocol, 1993, with various modifications through 1995.

47. See, for instance, Olivieri's report to Apotex with covering letter to Spino, dated 961115, in which she included tables showing HIC and serum ferritin data on patients during the post-trial close-out period after May 1996, as well as before May 1996.
48. Report by Olivieri, Cameron and Brittenham to regulators, incorrectly dated 970122, sent to regulators on 970224, provided to Koren, 970205, and to O'Brodovich, 970220—see especially the appended report by Cameron on the biopsy slides, in particular the parts on patients numbered 16 and 17. See also the report by Apotex's consultant Dr. Callea, 970524, provided by Dr. Spino to Drs. Freedman and Goldbloom with a covering letter on 970610, in which the biopsy records of the same patients were reviewed.
49. Letter, Berkovitch to Naimark, 980917 .
50. letter, Berkovitch to Haslam, 951120.
51. Letters, Moore to O'Brodovich, 970227 and 980603.
52. Summary of testimony by Moore to MAC, 990111—see section 5K(7) for a quotation from this summary.
53. Letter, Shin to Lacey, 000310.
54. Book, G. Koren ed., *Textbook of Ethics in Pediatric Research*, Krieger, Florida (1993). Koren lists the seven chapters he wrote in the CV he submitted to MRC in 1993, with the application for joint MRC-Apotex funding for the LA-03 trial.
55. E-mail, Aberman to Durie *et al.*, 980830.
56. Copies of all of these letters by Dr. Koren were submitted to the Naimark Review and indexed in its Report: i) Olivieri and Koren to Haslam, 960524; ii) Olivieri and Koren to Zlotkin, 960715; iii) Koren to Olivieri, 970815; iv) Koren to O'Brodovich, 971103; v) Koren to O'Brodovich, 971126; vi) Koren to Becker, 980415; and vii) Koren to Buchwald, 980514.
57. Letter, Koren to Roy, 981218.
58. Report of the *ad hoc* subcommittee of the MAC (undated), conveyed to Dr. Olivieri with a letter from Becker, 000118.
59. Report of the MAC, dated April 2000, released to the public in a press conference organized by the HSC, 000427.
60. Report of the *ad hoc* subcommittee of the MAC (undated), conveyed to Dr. Olivieri with a letter from Becker, 000118, p. 3.
61. Report of the *ad hoc* subcommittee of the MAC (undated), conveyed to Dr. Olivieri with a letter from Becker, 000118.
62. Letter, Becker to Olivieri, 000118.
63. Letters, Koren to Roy, 981218 and O'Brodovich to Roy, 990104; and summaries of testimony by Koren and by O'Brodovich, both on 990119.
64. Report of the *ad hoc* subcommittee to the MAC, p.7—conveyed to Olivieri, 000118 with letter by Becker.
65. Dr. Olivieri's three-volume response to the MAC included her correspondence with Dr. O'Brodovich and others, as well as her information to patients, from February and March 1997, in which she explained the clinical reasons why the patients were being counselled to have biopsies done. See in particular, MAC binder III, tabs 72, 75, 76, 78–86. It also included, at tab 60, her 1997 review article published in *Blood*, in which the role of biopsy as a guide to therapy was outlined, and supported by references to the recent literature.
66. Report of the *ad hoc* subcommittee to the MAC, p.7—conveyed to Olivieri, 000118 with letter by Becker.
67. Report of the *ad hoc* subcommittee to the MAC, p.7—conveyed to Olivieri, 000118 with letter by Becker.
68. Response to MAC by Olivieri, 991012: her brief, pages 38–43; and the supporting documents, including tabs 72, 84 which were copies of her letters to Dr. O'Brodovich dated February 20 and March 6, 1997 confirming that biopsies were being arranged and explaining the medical reasons. Also included at tab 71 was her report to the regulators, and tab 60 a copy of her 1997 review article in *Blood*.

69. Report (undated) of the *ad hoc* subcommittee to the MAC, p.2—conveyed to Olivieri, 000118 with letter by Becker.
70. Report (undated) of the *ad hoc* subcommittee to the MAC, p.3—conveyed to Olivieri, 000118 with letter by Becker.
71. Letter, Becker to Olivieri, 000118.
72. Letter, Shin to Lace, 000310.
73. Letter, Shin to Lace, 000310.
74. See the passage in Dr. Koren’s 1993 text, quoted in subsection 5P(8). In a letter to Dr. Buchwald dated 980415, Dr. Moore confirmed that until 1998, when the new *Tri-Council Policy Statement* came into force, chart review research did not require REB approval (see p. 2 of her letter).
75. Abstract, N. Olivieri and G. Brittenham, “Final results of the randomized trial of deferiprone (L1) and deferoxamine (DFO),” supplement to *Blood*, Dec. 1997.
76. Report (undated) of the *ad hoc* subcommittee to the MAC, p.2—conveyed to Olivieri, 000118 with letter by Becker.
77. Letter, O’Brodivich to Naimark, 981012, “Dr. Koren has provided me with a copy of the abstract submitted to the 1997 ASH meetings by Dr. Olivieri” This letter was not indexed in the Naimark Report and not deposited in the HSC library archive.
78. a) Memo, Hales (Director of Pharmacy, HSC) to O’Brodivich, 981026: “No prescriptions [for L1] have been filled for either inpatients or outpatients since that date [February 18, 1997].”
b) E-mail, Freedman to O’Brodivich, 970228: “Sue Carson, thalassemia nurse, confirmed that all 14 or so HSC pts on L1 have been taken off therapy. The rest of the L1 pts are at the General [TTH] and not in our jurisdiction; I’m told that some have stopped and others have refused to stop over there.”
79. See, for instance, the letter, Moore to Olivieri, 970430.
80. Letter, Klein to Koren, 981028—put forward to Naimark by O’Brodivich with covering letter, 981028, saying, “today I received a copy of a letter to you [sic—Klein’s letter was addressed to Koren] from Naomi Klein”
81. Letter, Klein to Koren, 981119—put forward to Naimark by O’Brodivich with covering letter, 981120.
82. Letter, Olivieri to Koren, 961028, copied to Klein.
83. Letter, N. Klein to O’Brodivich, 981217. This letter was in reply to one Dr. O’Brodivich sent her on 981126, that he copied to Koren. See also letters: O’Brodivich to Naimark, 981129; and Koren to O’Brodivich, 981126.
84. Statement by hepatopathologist R.G. Cameron, 990318, Olivieri’s submission to MAC, binder I, tab C.
85. Letter to HSC Board members and Provost Sedra, 980905; and statement by hepatopathologist R.G. Cameron, 990318.
86. Memo, Olivieri to O’Brodivich and Freedman, 970306; and information circular for patients distributed at meeting on 970306.
87. Letter, Becker to Olivieri, 000118; and MAC press release, 000427.
88. Memo, O’Brodivich to Naimark, 980924; letter, O’Brodivich to Roy, 990104.
89. Naimark Report, pp. 41 and 134; letter, Koren to Roy, 981218 and summary of oral testimony, Koren to MAC, 990119.
90. Interviews of Olivieri by CoI, 000304 and 000710.
91. Summary of testimony, Massicotte to MAC, 990209.
92. Public statement by Olivieri, 981210, headed: “To My Patients ...”
93. Letter, O’Brodivich to Roy, 990104, p. 2
94. Letter, O’Brodivich to Roy, 990104, p. 4.
95. Letter from Colangelo (joint CMPA legal counsel to Olivieri and Koren) to Olivieri and Koren, 970205, enclosing Olivieri’s full report of the newly identified risk of progression of liver fibrosis; and Humphrey report, 991220, p. 195.

96. Letter, Koren to Roy, 981218, pages 1 and 2; see also Naimark report, page 41, where letters put forward by Dr. Koren were reproduced.
97. Letter, Colangelo to Koren and Olivieri, 970205.
98. Summary of testimony, Koren to MAC *ad hoc* committee, 990119; and letter, Koren to Roy (MAC), 981218.
99. Letter, Koren to Roy, 981218.
100. Summary of testimony, Koren to MAC, 990119.
101. See sections 5G, 5H and 5P(8) for details and citations.
102. E-mail, Aberman to Durie *et al.*, 980830—with an account of mediation meeting on 960607; memo, Goldbloom to file, 961114—with an account of meeting on 961113 concerning supply of L1. See also letter, Koren to Becker, 980415, p. 2.
103. See letters by Koren to Olivieri (970815), O’Brodivich (971103 and 971126), Becker (980415) and Buchwald (970514).
104. Summary of testimony, O’Brodivich to MAC subcommittee, 990119.
105. Letter, Koren to Roy, 981218.
106. Letter, Becker to Olivieri, 000118; and HSC/MAC press release, 000427.
107. HSC/MAC press release, 000427.
108. Letters, Olivieri to O’Brodivich and to Moore, 970220. Memo, Hales to O’Brodivich, 981026. See also the letter, A. Kowalczyk (HSC pharmacy) to Massicotte, 990205, confirming that the last prescription for L1 was dated 970218. E-mail, Freedman to O’Brodivich, 970228, 1:26 PM, reporting information from Nurse Carson.
109. Information sheet, Olivieri to patients and parents, distributed at group information meeting, 970306.
110. Report by NIH expert panel, chaired by A. Cohen, “Cooley’s Anemia: Progress in Biology and Medicine—1995,” published by NIH in 1995. See also review article, N.F. Olivieri and G.M. Brittenham, *Blood*, 89, 3 (Feb. 1, 1997), pp. 739–761 (see esp. pages 740, 743, 747–750), and relevant references cited therein. The relevant facts were outlined by Olivieri in the information sheet for the meeting of 970306 with patients and parents.
111. See: Dr. O’Brodivich’s September 24, 1998 memo to Dr. Naimark in which he devotes a substantial paragraph to a favourable summary of the report of Apotex’s consultant, Dr. Callea, who stated that L1 did not cause progression of liver fibrosis; and Dr. Koren’s article on L1 in *Therapeutic Drug Monitoring (1999)* (submitted in August 1998), in which no mention is made of the risk of L1 of progression of liver fibrosis.
112. Letter, Stockwood to Lace, 000426.
113. Application for ethical approval of proposed study of L1 in SCD, Olivieri to REB, August 1996 (see p. 47 of Olivieri’s 991012 brief to MAC), endorsed by O’Brodivich on 970122.
114. Brief, Olivieri to MAC, 991012, p. 47.
115. Letter, Olivieri to Moore, 970220.
116. Letter, Moore to Olivieri, 970224.
117. Letter, O’Brodivich to Moore, 970226.
118. Minutes, REB of HSC, 970214.
119. Letter, Olivieri to Joshi (REB reviewer for the proposal), 970307.
120. Response by Olivieri to MAC, 991012, brief, pp. 46–49.
121. Response by Olivieri to MAC, 991012, brief, pp. 46–49.
122. Response by Olivieri to MAC, 991012, brief, pp. 46–49.
123. Response by Olivieri to MAC, 991012, brief, pp. 46–49.
124. Letter, Moore to Joshi, 971217.
125. Letter, Symes to Stockwood, 990111.
126. Letter, Symes to Stockwood, 990111.
127. Letter, Symes to Stockwood, 990111.
128. Letter, Symes to Stockwood, 990111.
129. Letter, Becker to Olivieri, 000118, enclosing undated report of *ad hoc* subcommittee.
130. Letter, Becker to Olivieri, 000118.

131. Letter, Roy to Olivieri, 981223.
132. Letter, Shin to Lace, 000310.
133. Letter, Lace to Stockwood, 000330.
134. Letter, Lace to Stockwood, 000330.
135. See MAC report to the Board dated “April 2000,” included with material released to the media on 000427; and letter Lace to Stockwood, 000330.
136. Discussion between CoI and Lace re: MAC proceedings, 000825.
137. Testimony of Olivieri to CoI, 000424.
138. Letter, Stockwood to Lace, 000426—Ms. Lace reported to this Committee of Inquiry on 000825 that this letter arrived at her firm by fax after 5:00 PM on 000426.
139. HSC media release, 000427.
140. Letters: Becker to Complaints Committee of CPSO, 000502; and Becker to Phillipson (Chair, UT Dept. of Medicine), 000502.
141. Testimony of Olivieri to CoI.
142. Letter, Baker to Spino, 970417; and testimony by Baker to CoI, 991215.
143. Olivieri’s treatment protocols were outlined in the review article, N.F. Olivieri and G.M. Brittenham, *Blood*, 89, 3 (Feb. 1, 1997), pp. 739–761. Treatment differences depending on patients’ ages were discussed in the article.
144. In his letter dated 990104 to the MAC, Dr. O’Brodivich noted that Dr. Olivieri had consulted with Dr. Baker (who is a hematologist) on patient care during the period in question. In her October 12, 1999 submission to the MAC, Dr. Olivieri included the letter, Baker to Spino, 970417, at tab 88, binder III.
145. See: letter, Spino to A. Klein (HPB, Health Canada), 960813.
146. Priority Review Submission by Apotex Research Inc. to HPB, Health Canada, 970930. In this submission, L1 was referred to by the trade name “Deferrum.”
147. In its 1998 submission to the Canadian regulatory agency, HPB, L1 was referred to by the trade name “Exferrum,” instead of the trade name “Deferrum” used in Apotex’s 1997 Priority Review Submission to HPB. L1 was referred to as “Ferriprox” in Apotex’s European licencing submission.
148. Letter, Spino to O’Brodivich, 980522.
149. Letter, Prichard and Strofolino to Koren, 000411.
150. Article, *National Post*, 000415, referring to an announcement on 000414 by HSC and the University.
151. Statements of Defence and Counterclaim by Sherman and Apotex, 000619, par. 78; and Statement of Defence and Counterclaim by J. Kay and Apotex, 000724, par. 81—filed in an Ontario court. After the April 7, 2000 decision by European Court of Justice allowing Dr. Olivieri’s application for judicial review of Apotex’s restricted licence for L1 to proceed on the merits (see section 5.U), Apotex made a submission to the Court in which it relied on: i) findings against Dr. Olivieri in the Naimark Report; ii) HSC’s referral of Dr. Olivieri to the CPSO and the University of Toronto; and iii) Dr. Koren’s scientific opinions on L1. The relevant documents were not available to us under procedures of the Court—the foregoing summary was provided by Ms. Lori Stoltz, counsel for Dr. Olivieri, on behalf of her client, in response to our request for information.

Notes to Section 5Q: The MAC Allegations in regard to Liver Biopsies

1. Letter, Koren to Roy (MAC), 981218 and summary of testimony, Koren to MAC, 990119.
2. Letter, O’Brodivich to Roy (MAC), 990104 and summary of testimony, O’Brodivich to MAC, 990119.
3. N.F. Olivieri and G.M. Brittenham, review article, “Iron-chelating therapy and the treatment of thalassemia,” *Blood, the Journal of the American Society of Hematology*, 89, 1, (Feb. 1, 1997), p. 741.

4. E. Angelucci *et al.*, "Needle liver biopsy in thalassemia: analyses of diagnostic accuracy and safety in 1184 consecutive cases," *British Journal of Haematology*, 89 (1995), pp. 757–761.
5. D.J. Weatherall and J.B. Clegg, *The Thalassemia Syndromes*, 3rd ed., Blackwell, Oxford (1981), p. 157; and N.F. Olivieri, review article, "The β -Thalassemias," *The New England Journal of Medicine*, 341, 2 (July 8, 1999), p. 103.
6. N.F. Olivieri, review article, "The β -Thalassemias," *The New England Journal of Medicine*, 341, 2 (July 8, 1999), p. 105.
7. N.F. Olivieri and G.M. Brittenham, review article, "Iron-chelating therapy and the treatment of thalassemia," *Blood, the Journal of the American Society of Hematology*, 89, 1, (Feb. 1, 1997), p. 742.
8. Report of the Cooley's Anemia Progress Review Committee chaired by A. Cohen, titled, *Cooley's Anemia: Progress in Biology and Medicine – 1995*, published by NIH (1995), p. 25.
9. See the article by A.V. Hoffbrand, B. Wonke *et al.*, "Long-term trial of Deferiprone [L1] ...," *Blood*, 91, 1 (January 1, 1998), p. 295–300. The authors used monthly measurements of serum ferritin concentrations to assess efficacy of L1, but after several years compared the results with liver iron concentrations obtained by biopsy. They found that, "serum ferritin concentration is a relatively inaccurate measure of body iron burden compared with liver iron estimation." (See pages 297 and 298 of this article.)
10. N.F. Olivieri, review article, "The β -Thalassemias," *The New England Journal of Medicine*, 341, 2 (July 8, 1999), p. 106.
11. Testimony of Olivieri to CoI, February and July 2000.
12. Statement by Cameron, 990318, submitted to MAC by Olivieri on 991012.
13. The index of documents in the Naimark Report lists four letters: Spino to Brittenham, N 231, 970306; Brittenham to Spino, N 232, 970306; Spino to Brittenham, N 235, 970307; and Brittenham to Spino, N 237, 970310. None of these were deposited in HSC archives, but the two letters from Spino to Brittenham were available to this Inquiry. The Naimark Report index summarized the contents of the letters from Brittenham to Spino as follows. N 232: "suggesting Brugge an ideal opportunity to alert physicians in Europe; and asking if Apotex has objections or plans to bar presentation." N 237: "Invites Spino to attend meeting at Brugge and present the Apotex assessment of the hepatic toxicity issue."
14. This quotation from Dr. Brittenham's letter to Dr. Spino of 970306 is contained in Dr. Spino's letter of reply, Spino to Brittenham, 970307.
15. Letter, Spino to Brittenham, 970307.
16. Letter, Spino to Olivieri, 970827.
17. "Priority Review Submission" by Apotex to HPB for "Deferrum," 970930—only parts of this document are available, obtained by an 'access to information' request under the *Privacy Act*.
18. Apotex Research document titled, "Comprehensive Summary—Exferrum [an Apotex trade name for L1]," dated 980130, pp. 50–51.
19. Apotex Research document titled, "Comprehensive Summary—Exferrum [an Apotex trade name for L1]," dated 980130, pages 46–47.
20. Letter, Spino to O'Brodovich, 980522.
21. Abstract, Olivieri and Brittenham to ASH, December 1997 meeting, published in Dec. 1997 supplement to *Blood*.
22. Letter, Spino to O'Brodovich, 980522.
23. It was only in 1998, when the new Tri-Council ethics policy came into force, that publication based on chart review required REB approval. See section 3A of this report. See also: (i) letter, Moore to Buchwald, 980415; and (ii) minutes of REB meeting, 980517.
24. letter, Spino to Naimark, 981124, pp. 3, 4.
25. Letter, Koren to Roy (MAC), 981218.
26. Letter, Koren to Roy (MAC), 981218, quoting letter, Moore to O'Brodovich, 980603.

27. Letter, Koren to Roy (MAC), 981218.
28. Summary of testimony, Koren to MAC.
29. Letter, O'Brodovich to Roy (MAC), 990104.
30. Sentence quoted by O'Brodovich in his letter to Roy, 990104—the sentence is from the article, P. Tondury *et al.*, “Liver iron and fibrosis during long-term treatment with deferiprone in Swiss thalassaemic patients,” *Br. J. Haem.*, 101 (1998), pp. 413–415.
31. Article, P. Tondury *et al.*, “Liver iron and fibrosis during long-term treatment with deferiprone (L1) in Swiss thalassaemic patients,” *British J. Haematology*, 101 (1998) pp. 413–415.
32. Dr. Cameron and Dr. Callea (the liver pathologist hired by Apotex) came to opposite conclusions on the question of progression of fibrosis in the former LA–03 cohort, but they both agreed that, for this group, hepatitis C status was not statistically significant to their findings respecting fibrosis status.
33. Article, P. Tondury *et al.*, “Liver iron and fibrosis during long-term treatment with deferiprone (L1) in Swiss thalassaemic patients,” *British J. Haematology*, 101 (1998), p. 414.
34. Article, P. Tondury *et al.*, “Liver iron and fibrosis during long-term treatment with deferiprone (L1) in Swiss thalassaemic patients,” *British J. Haematology*, 101 (1998), p. 415.
35. Patient Information Form, LA–03 trial, undated, included in Olivieri’s submission to MAC, 991012, volume II, tab 8.
36. E. Angelucci *et al.*, “Needle liver biopsy in thalassemia: analyses of diagnostic accuracy and safety in 1184 consecutive cases,” *British Journal of Haematology*, 89 (1995), pp. 757–761.
37. E. Angelucci *et al.*, “Needle liver biopsy in thalassemia: analyses of diagnostic accuracy and safety in 1184 consecutive cases,” *British Journal of Haematology*, 89 (1995), pp. 757–761.
38. N.F. Olivieri and G.M. Brittenham, review article, “Iron-chelating therapy and the treatment of thalassemia,” *Blood, the Journal of the American Society of Hematology*, 89, 1, (Feb. 1, 1997), p. 747.
39. Humphrey Report, p. 195; and Naimark Report, p. 41.
40. Report by Olivieri, Cameron and Brittenham to regulators, dated “January 22, 1997,” but not completed and signed until February 1, 1997—sent to Apotex on 970204 and Koren on 970205.
41. Letter to *The Lancet* by Ciba staff scientists, vol. 341 (930424), p. 1088.
42. MRC application by Olivieri and Koren, 1990; and 1990 protocol for the long-term phase of pilot study.
43. 1990 protocol for the long-term phase of pilot study.
44. LA–01 protocol, originally dated May 1993, last revised in October 1995.
45. LA–03 protocol, dated March 1991, revised in October 1993 and September 1995.
46. *Food and Drugs Act and Regulations*, Canada, section C.08.010.
47. Letter, Oliveri and Koren to Zlotkin, 960715.
48. Report by the *ad hoc* subcommittee of the MAC to the MAC, undated but conveyed to Olivieri by Becker on 000118, page 7.
49. EPAR issued by the EMEA of the Commission of the European Communities, 990825.
50. Article, N.F. Olivieri *et al.*, *The New England Journal of Medicine*, 339, 7 (August 13, 1998).
51. N.F. Olivieri, review article, “The β -Thalasseмииs,” *The New England Journal of Medicine*, 341, 2 (July 8, 1999).
52. N.F. Olivieri and G.M. Brittenham, review article, “Iron-chelating therapy and the treatment of thalassemia,” *Blood, the Journal of the American Society of Hematology*, 89, 1, (Feb. 1, 1997).
53. Interviews by CoI of Weatherall, 991031, and Nathan, 991103.

54. Letter, Aberman to Phillips, 971001.

Notes to Section 5R: The Central Role of Dr. Koren in the L1 Controversy

1. Report by HSC's investigator, Ms. Barbara Humphrey, "Re: Investigation of Harassment Complaint" against Dr. Koren by Dr. Olivieri *et al.*, 991220, p. 227. Ms. Humphrey interviewed Dr. Koren, Dr. Olivieri, and others involved in the L1 controversy, and she reviewed many documents, as well as evidence by forensic experts.
2. Humphrey Report, 991220.
3. Humphrey Report, 99 1220 .
4. Memo, HSC Executive to medical and scientific staff, 980901.
5. Letter, Aird to Chan *et al.*, 991210.
6. Formal complaint by Dr. Chan *et al.* lodged with HSC and UT, 990517—a binder consisting of a written brief with many attachments, including 4 of the 5 anonymous letters and forensic reports. The 5th anonymous letter was sent 9905 14, but received a few days later)—this 5th letter and a report by a forensic expert dated 990603 on it were also submitted as a supplement to the complaint lodged in May 1999. Quotations from the anonymous letters are taken from the copies of the letters in the complaint documents. The copy of the complaint available to us is undated, but the Humphrey report, Page 1, confirms the date of 990517.
7. Formal complaint by Dr. Chan *et al.* lodged with HSC and UT, 990517 and material on the 5th letter, submitted in June 1997.
8. Formal complaint on the first four letters by Dr. Chan *et al.* lodged with HSC and UT, 990517 and material on the 5th letter, submitted in June 1997.
9. Humphrey report, 991220 .
10. Humphrey report, 991220.
11. Humphrey report, 991220.
12. Humphrey Report, 991220.
13. Humphrey Rreport, 991220.
14. Humphrey Rreport, 991220.
15. Humphrey Rreport, 991220.
16. Humphrey Report, 991220.
17. Humphrey Rreport, 991220.
18. Humphrey Report, 991220.
19. The anonymous letter to Dr. Durie, 981021.
20. *Globe and Mail*, 991221; *National Post*, 991221 .
21. Several Toronto newspapers (for instance, the *Globe and Mail*) reported on the suspension, imposed 991221, in articles dated 991222.
22. Information by Dr. Chan *et al.* and UTFA in interviews with this committee.
23. *National Post*, 000415; *Star*, 990504; *Nature Medicine*, vol. 6, no. 6 (June 2000), pp. 609–610.
24. Letter, Prichard and Strofolino to Koren, 000411.
25. Letter, Prichard and Strofolino to Koren, 000411.
26. Letter, Prichard and Strofolino to Koren, 000411, pp. 6–7.
27. Letter, Prichard and Strofolino to Koren, 000411, pp. 8–9.
28. Letter, Prichard and Strofolino to Koren, 000411, p. 9.
29. Letter, Prichard and Strofolino to Koren, 000411, p. 2.
30. O. Diav-Citrin, A. Atanackovic, and G. Koren, "An investigation Into Variability of the Therapeutic Response to Deferiprone in Patients With Thalassemia Major," *Therapeutic Drug Monitoring*, 21 (1999), pp. 74–81. The article was received by the journal on

980812, and accepted for publication on 981006.

31. O. Diav-Citrin, A. Atanackovic, and G. Koren, "An investigation Into Variability of the Therapeutic Response to Deferiprone in Patients With Thalassemia Major," *Therapeutic Drug Monitoring*, 21 (1999), p. 74.
32. Letter, Koren to Becker (Chair, MAC), 980415.
33. Letter, Koren to Buchwald (Director, Research Inst.), 980511.
34. Letter, Koren to Buchwald (Director, Research Inst.), 980511.
35. Note, Gidi [Koren] to Manuel [Buchwald], 980514 .
36. Abstract by O. Diav-Citrin, G. Atanackovic, R. Loebstein and G. Koren, "Investigation of variability in response to deferiprone (L1) in patients with β -thalassemia major," *Clinical Pharmacology and Therapeutics*, abstract # PI-38, February 1997, p. 146.
37. "Minutes-notes" by Koren, of a meeting on 980513, at which Koren, Diav-Citrin, Spino and Tricta were listed as attending, dated 980514.
38. "Minutes-notes" by Koren, of a meeting on 980513, at which Koren, Diav-Citrin, Spino and Tricta were listed as attending, dated 980514. The principle measure of efficacy in the long-term trial (LA-03) was hepatic iron concentration (HIC), measured either by chemical assay of biopsy specimens or by magnetic susceptometry (SQUID). Because of the very high correlation established in the 1980s by Dr. Brittenham and others, the two were used interchangeably.
39. O. Diav-Citrin, A. Atanackovic, and G. Koren, "An investigation Into Variability of the Therapeutic Response to Deferiprone in Patients With Thalassemia Major," *Therapeutic Drug Monitoring*, 21 (1999), p. 75.
40. See, for instance, "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" established by the International Committee of Medical Journal Editors (1994); the University of Toronto *Framework for Ethical Conduct of Research and Guidelines to Address Research Misconduct* (1996); and the University of Toronto Policy on Conflict of Interest, Academic Staff (1994).
41. Letter, Prichard and Strofolino to Koren, 000411, p. 1.
42. Humphrey Report, 991220.
43. Humphrey Report, 991220 .
44. Letter, Prichard and Strofolino to Koren, 000411, p. 4, 5.
45. Naimark Report.
46. See sections 5K, 5O, 5P, and 5Q for detailed discussions and citations of source documents.
47. Letter, Koren to Roy (MAC), 981218.
48. Summary of testimony, O'Brodovich to MAC *ad hoc* subcommittee, 990119.
49. Letter, Koren to Roy (MAC), 981218.
50. Summary of testimony, Koren to MAC *ad hoc* subcommittee, 990119 .
51. E-mail, Dick to Phillips, 971001, reporting on recent conversation with Koren.
52. Humphrey Report, 991220.
53. Humphrey Report, 991220.
54. Memo, Koren to Olivieri, 970815. See also letter, Koren to O'Brodovich, 971126.
55. Letter, Koren to Buchwald, 980511.
56. Note, Gidi [Koren] to Manuel [Buchwald], 980514.
57. Letter, Olivieri and Koren to Zlotkin, 960715.
58. Note, Koren to Buchwald, 980514.
59. Letter and attached data reports, Olivieri to Spino, copied to Koren and Aberman, 961115.
60. Letter, Spino to Koren, 971023, copied to Dr. O'Brodovich and others.
61. Letter, Koren to O'Brodovich, 971103.

Notes to Section 5S: Involvement of the CAUT and the UTFA

1. See, for instance: minutes of the UT Governing Council, 981105, p. 10; and public statement by the University, 981203 (quoted in section 5N of this report).

2. Article, *CAUT Bulletin*, September 1998, p. 1.
3. The Report of the UT Academic Board, 981008, p. 7 dates this meeting at which Drs. Sedra and Gooch “briefed UTFA” as “early September.” Ms. Hudgins in her testimony to CoI dates the meeting as “August 26.”
4. Testimony of Hudgins to CoI; see also letter, Hudgins to Thompson (CoI), 010330 (in Appendix G to this report).
5. Testimony of Love to CoI.
6. Testimony of Turk (CAUT), and Love and Hudgins (UTFA) to CoI, in 1999 and 2000.
7. Press release by CAUT, 981124.
8. Article, *Globe & Mail*, 981102, discussing efforts by the “salvage group.” See also section 5.O.1 of this report.

Notes to Section 5T: Public Interest, Public Policy, Contracts & Legal Representation

1.
 - a) In a public statement on December 9, 1998 President Prichard said, “The University’s pre-eminent obligation is to ensure the academic freedom of all of its members, wherever they work. ... Recent events underscore the importance of the university speaking out in support of the fundamental freedoms of the university, not only to support individual colleagues, but to create an environment in which all faculty members have confidence they will be protected from improper pressure from any quarter.”
 - b) “The pre-eminent concern of the Board of Trustees of the Hospital for Sick Children in commissioning the LI Clinical Trials Review was the safety and welfare of the children whose care and treatment took place at or under the aegis of the Hospital.”—Naimark Report, page 87, released 981209.
2.
 - a) Smyth, Soberman, Easson, *The Law and Business Administration in Canada* (8th ed.). Toronto: Prentice-Hall (1998)
 - b) S.M. Waddams, *The Law of Contracts* (4th ed.). Toronto: Canada Law Book Inc. (1999).
3. Letter, Soberman to Thompson (CoI), 000321—see Appendix F.
4. Letter, Soberman to Thompson (CoI), 000321—see Appendix F.
5. This conclusion would apply also to the confidentiality clause in the LA-02 consulting contract, in the event Apotex sought to have it enforced to prevent disclosure of risks. (See section 5B.)
6.
 - i) news item in *Med.E.Mail*, newsletter of the UT Dean of Medicine’s office, 010326; ii) Toronto Star, 010327, quoting Dean Naylor.
7. Letter, Olivieri and Koren to Haslam, copied to Aberman, 960525.
8. Letter, Goldbloom to Olivieri, 971028; and Naimark Report, p. 145.
9. “What is the CMPA?”—from the website, cmpa.org.
10. Interview of Mason by CoI, 001216; and letter, Colangelo to O’Brodivich, 970228.
11. LA-03 contract, signed by Spino, 951002, Koren, 951010, and Olivieri, 951012.
12. Draft letter, Gertner to Olivieri, 960802. We do not know whether this letter was actually sent to Dr. Olivieri, or to the CMPA. In any case, the CMPA wrote to her a few days later expressing the same opinion—letter, Lee (CMPA) to Olivieri, 970807.
13. Letter, Lee (CMPA) to Olivieri, 970807.
14. Letter, Lee (CMPA) to Olivieri, 970807.
15. Letter, Olivieri *et al.* to Sedra (UT provost) and HSC Board, 980905—Dr. Olivieri met with CMPA officials in Ottawa on 960814, while there for her meeting with HPB.
16. Letter, Mason to Gertner, 960719.
17. Letter, Colangelo to Kay, 960819.
18. Letter, Brown to Colangelo, 970211.
19. Interview of Mason by CoI, 001216. Articles in *Fortune* magazine, 990906 and the *Globe*

& Mail Report on Business magazine, September 1996 comment on Apotex's use of litigation.

20. Letter, Colangelo to O'Brodovich, 970228; and interview of Mason by CoI, 001216.
21. Interview of Mason by CoI, 001216.
22. Memo, Colangelo to file, 970227. Referring to information he received the morning of February 27, 1997, Mr. Colangelo wrote, "This morning I met with Dr. Olivieri and .. Dr. Stan Zlotkin and Dr. Aideen Moore. ... One fact I had not previously appreciated is that on February 4, 1997, Dr. Olivieri spoke with all of the patients about her new findings and had informed them of the risks and benefits of continuing with treatment and of not continuing with treatment."
23. Letter, Olivieri to Colangelo, 970304.
24. Memo, Mason to file, 960719 (notes from meeting the day before involving Olivieri, Koren, Goldbloom, O'Brodovich and Mason).
25. Memo, Clements (B&E) to HSC administrator Ms. Anne Marie Christian, 971028.
26. Memo, Clements (B&E) to HSC administrator Ms. Anne Marie Christian, 971028.
27. Memo, Clements (B&E) to HSC administrator Ms. Anne Marie Christian, 971028.
28. Public statement by the University, 981203, web-posted 981215.
29. Agreement among HSC, UT and Olivieri, 990125.
30. Letter, Aird to Olivieri, 000209.
31. Statement of Defence and Counterclaim by Sheman and Apotex, 000619.
32. Letter, Strofolino to Mitchell (counsel for Olivieri), 010108.

Notes to Section 5U: The Involvement of Government Regulatory Agencies

1. Canada, *Food and Drugs Act and Regulations*, Section C—Drugs, division 8, sections C.08.005. (2) and C.08.005.1 (4) and (5).
2. In a letter, Spino to A. Klein (HPB) sent August 13, 1996, the day before Olivieri's meeting with HPB, Spino indicated that Apotex was using communications among lawyers to deter Olivieri from meeting with HPB (copy letter obtained by Olivieri from HPB). In another letter, sent August 14, 1996, Apotex issued a further legal threat, specifically warning Dr. Olivieri against meeting with HPB (letter, Kay to Colangelo, 970814).
3. Memo, I. Hynie (HPB) to T. Uscinowicz (HPB), undated but refers to the article in *The Medical Post*, 970121 on Dr. Olivieri's presentation to ASH, December 1996.
4. Memo, A. Klein (HPB) to T. Uscinowicz (HPB) and copied to I. Hynie (HPB), 970602.
5. Review article, N.F. Olivieri and G.M. Brittenham, *Blood*, 89, 3 (February 1, 1997); also, letter and attachments from Brittenham, Olivieri and Cameron to Fredd (FDA) with copies to HPB and other regulatory agencies, and to Apotex, dated 970122, but not sent until 970204 (to Apotex) because Cameron wished to check his results, and not sent to the regulators until 970224, because of legal warnings from Apotex.
6. The report referred to by A. Klein of HPB is the letter and attachments from Brittenham, Olivieri and Cameron to Fredd (FDA) with copies to HPB and other regulatory agencies, dated 970122, but not sent to the regulators until 970224, because of legal warnings from Apotex.
7. (i) It appears from an Apotex document partially disclosed following an application under the *Privacy Act*, that the date of the Apotex "new drug submission" to HPB was on or about January 30, 1998.
(ii) In an internal HPB memo, A.V. Klein to F. Iverson, dated 980421, there is reference to the Apotex submission and a meeting with Apotex "a few weeks ago" concerning it.
(iii) It also appears from another Apotex document partially disclosed following an application under the *Privacy Act* that Apotex had earlier made a "Priority Review Submission," on or about September 30, 1997.

8. Olivieri's report to the FDA and HPB, along with the regulatory agencies in Italy and India was sent on 970224.
9. Memo, A. Klein (HPB) to F. Iverson (HPB), 980421.
10. N.F. Olivieri *et al.*, *New England Journal of Medicine*, 339, 7 (August 13, 1998).
11. Memo, O. Pulido, MD and R. Mueller, DVM to A. Klein, 980917.
12. Priority Review Submission by Apotex Research Inc. to HPB, dated 970930—excerpts made available through an application under the *Privacy Act*.
13. Apotex documents on L1 submitted to HPB, dated 980126 and 980130—excerpts made available through an application under the *Privacy Act*; the European Public Assessment Report on L1, dated 990825, gives 980206 as the date of Apotex's application for a Marketing Authorisation in Europe.
14. "Comprehensive Summary (Exferrum)", dated 980130, an Apotex Research document prepared in connection with a submission to the Australian regulatory agency, pp. 50, 51. "Exferrum" is a term Apotex has used for its formulation of L1.
15. "Comprehensive Summary (Exferrum)", dated 980130, an Apotex Research document prepared for its submission to the Australian regulatory agency, pages 50, 51. See also the European Public Assessment Report on L1 dated 990825, Scientific Discussion section, subsection 4, page 7/11, discussion of the LA-01 trial in Toronto.
16. A document titled "Clinical Study Report LA-01 Comparative study of Exferrum (L1) and DFO (deferroxamine)," submitted by Apotex to HPB, 980126—excerpts obtained through an application under the *Privacy Act*—states: "These (protocol) violations were the primary reason the Sponsor decided to terminate the study at the Toronto sites on May 24, 1996." This 1998 "primary reason" for terminating this trial and the LA-03 trial was new and different from the reason Apotex gave in 1996 when it took the action (see section 5F).
17. "Comprehensive Summary (Exferrum)", dated 980130, prepared by Apotex Research in support of a licencing application the Australian regulatory agency—copy given to Olivieri at a conference in Australia in July 1998. "Exferrum" is a term Apotex has used for its formulation of L1.
18. (i) "Comprehensive Summary," Apotex to regulators, dated 980130, pp. 50, 51 (in this licensing application, the Apotex formulation of L1 is termed "Exferrum"); and (ii) document by Olivieri (undated) providing an analysis of the "Comprehensive Summary" (dated 980130), p. 9.
19. N.F. Olivieri and G.M. Brittenham, "Final results of the randomized trial of deferiprone (L1) and deferroxamine (DFO)," supplement to *Blood*, December 1997, abstract# 1161.
20. Letter, Spino to Olivieri, 970827.
21. Letter, Spino to Olivieri, 970827.
22. Priority Review Submission by Apotex Research Inc. to HPB, dated 970930—excerpts made available through an application under the *Privacy Act*.
23. Letter, Spino to Olivieri, 970827.
24. Letter, Spino to Olivieri, 970827.
25. Protocol for LA-01 trial, originally prepared May 1993, with later modifications, the last on October 5, 1995. See page 11 of the October 5, 1995 protocol and the July 1995 modification appended to this protocol.
26. Contract for LA-01, dated 930423.
27. Letter, Spino to Brittenham, 960617.
28. Letter, Spino to Olivieri, 961127.
29. Letter, Spino to Olivieri, 961127; testimony of Brittenham to CoI, 000719.
30. Letter, Spino to Olivieri, 961127; testimony of Brittenham to CoI, 000719.
31. "Priority Review Submission" by Apotex to regulators, dated 970930, excerpts obtained through application under the *Privacy Act*.
32. Protocol modification # 6 for LA-01, signed by Spino on 950731.
33. Especially, severe neutropenia or agranulocytosis, due to bone marrow suppression — see

- letter to editor of *The Lancet* by Ciba-Geigy staff, vol. 341 (April 24, 1993), p. 1088.
34. N.F. Olivieri *et al.*, *New England Journal of Medicine*, 332, 14 (April 6, 1995), p. 922.
 35. Letter, Spino to Olivieri, 960214.
 36. Letter, Olivieri to Spino, 960212, enclosing report intended for REB.
 37. Letter, Spino to Olivieri, 960214.
 38. “Comprehensive Summary (Exferrum)”, dated 980130, an Apotex Research document prepared for its submission to the Australian regulatory agency, pp. 51 and 78.
 39. Informed Consent Form, appended to LA-02 protocol, dated 940623.
 40. Letter, Spino to Strofolino, 980931, 6 pages (see especially pages 1-3 for allegations concerning protocol violations). Apotex sent a copy of this letter to HPB on 980903, with a covering letter, Hems (Apotex) to Klein (HPB), 980903.
 41. Memo, HSC Exec. to HSC staff, 980901, page 1. (See section 5L(8).).
 42. European Public Assessment Report (EPAR), Committee for Proprietary Medicinal Products, European Agency for the Evaluation of Medicinal Products, Commission of the European Communities, 990825—referred to as “EPAR”.
 43. L1 was licenced for sale in India in 1995—see review article, N.F. Olivieri and G.M. Brittenham, *Blood*, 89, 3 (February 1, 1997), p. 753.
 44. EPAR, 990825.
 45. EPAR, 990825.
 46. Press release by Apotex, 990826.
 47. Article, *Globe and Mail*, 990827.
 48. (i) decision by the Court of First Instance of the European Communities, Luxembourg, in the case of Nancy Fern Olivieri against The Commission of the European Communities, issued 000407; and (ii) *National Post* article, 000408.
 49. (i) CV of Brill-Edwards; (ii) written “Opinion” by Brill-Edwards, 990424: testimony by Brill-Edwards to CoI, 991216 and 000204.
 50. The noncompliant patients were those who were unwilling or unable to accept the deferoxamine treatment regime, involving subcutaneous infusion many hours several days each week. The majority of those unwilling were teenagers. The sociological reasons for poor compliance among teenaged patients are outlined in D.G. Nathan, *Genes, Blood and Courage*, Belknap Press, Cambridge, Mass. (1995). See also written “Opinion” by Brill-Edwards, 990424.
 51. Written “Opinion” by Brill-Edwards, 990424.
 52. Written “Opinion” by Brill-Edwards, 990424.
 53. Written “Opinion” by Brill-Edwards, 990424.
 54. Written “Opinion” by Brill-Edwards, 990424.
 55. Written “Opinion” by Brill-Edwards, 990424.
 56. Transcript of the tape of the meeting between Olivieri *et al.* and Losos *et al.* of HPB, Ottawa, 990630.
 57. Letter, anonymous to Brill-Edwards, and envelope postmarked 990705.
 58. Handwritten letter, Koren to Brill-Edwards, 990711 and hand-addressed envelope.
 59. Letter, Brill-Edwards to Naylor, 000331.
 60. Letter, Brill-Edwards to Naylor, 000331.
 61. Testimony of Brill-Edwards to CoI, 991216 and 000204.
 62. Testimony of Brill-Edwards to CoI, 991216 and 000204.
 63. Humphrey Report, pp. 43–44, 53, 76–79.
 64. Testimony by Chan to CoI.
 65. Report, Helix Biotech to Gallie, 991207.
 66. Letter, Grinstein to Brill-Edwards, 981016, with a long appendix repeating the position of the HSC Executive and envelope.
 67. Letter, Grinstein to editor, *The Medical Post*, 981027.
 68. Report, Helix Biotech to Brill-Edwards, 000218.
 69. Letter, Brill-Edwards to Naylor, 000331.

70. *Globe&Mail*, 000505; *Nature Medicine*, May 2000.
71. E-mail, Naylor to staff of the HSC Research Institute, 000515, forwarded to staff by Christian (HSC) at Naylor's request.

Appendix A

Procedural Protocol Committee of Inquiry

**Re: Dr. Nancy Olivieri,
The University of Toronto,
The Hospital for Sick Children and
Apotex, Inc.**

A Committee of Inquiry has been established by the Canadian Association of University Teachers (CAUT) to inquire into allegations made by Dr. Nancy Olivieri. This action by the CAUT was taken at the request of Dr. Olivieri, with the support of the University of Toronto Faculty Association. The allegations involve matters listed in the terms of reference provided to the committee by the CAUT, which are attached.

The Committee of Inquiry will follow the procedural guidelines set out in the Policy Statement on CAUT Committees of Inquiry and Investigating Committees, except as modified for the purposes of this inquiry by motions of the CAUT Executive Committee. These motions confirm the independence of this Committee of Inquiry by eliminating the draft report stage in the policy and eliminating provisions for CAUT editorial control on the report, in addition to ensuring that the complete report will be published.

Consistent with these modified guidelines, the Committee is proceeding in the following manner.

1. The Committee will seek to review fully and fairly the allegations it has been appointed to investigate and prepare a written report to the AF&T Committee of CAUT on the matters covered by its terms of reference.
2. The Committee has no statutory powers and no authority to compel individuals to participate in the inquiry and, accordingly, relies upon the cooperation of everyone concerned to ensure that it is fully informed with regard to the matters under review. Anyone who chooses to be interviewed by the committee may be accompanied by a colleague.
3. The Committee will begin by reviewing the documentary record available to it upon its appointment, and will seek further information from individuals in a position to have relevant information by inviting them to meet with it and to submit documents.
4. The Committee will endeavour to consult with Dr. Olivieri, the President of the University of Toronto, the President of the Hospital for Sick Children, representatives of Apotex, Inc. and the President of the Faculty Association as

to information and sources of information, including documents and the names of persons to whom invitations for interviews should be sent.

5. Persons interviewed by the Committee will be provided with a statement of matters under investigation in advance of the interview. Persons interviewed will be permitted to make a statement to the Committee and to raise issues that they consider relevant, subject to the right of the Committee to decide, having provided an opportunity for arguments to the contrary, that particular matters are not relevant to its terms of reference.
6. Committee members will be taking handwritten notes during interviews, but interviews will not be recorded verbatim.
7. To ensure fairness to persons potentially affected in a material adverse way by findings in the committee's report, a fair summary of the information upon which such findings could be based will be provided in confidence to such persons reasonably in advance of the publication of the committee's report.
8. At any stage in its inquiry, the Committee in its discretion may request further information or clarification from individuals who have been interviewed or made written submissions, from those mentioned by witnesses or in submissions, or from other persons, by way of either a written statement or a meeting with the Committee.
9. The report of the Committee of Inquiry will be published by the CAUT, in its entirety, as delivered and in a timely fashion, provisions of the Policy Statement (including paragraphs 8–11) notwithstanding.

January 13, 2000

APPENDIX B

Persons Who Participated in the Inquiry

Dr. Michael Baker	The Toronto Hospital, University Health Network The Toronto Hospital
Dr. Michèle Brill-Edwards	Columbia University
Dr. Gary Brittenham	Hospital for Sick Children
Dr. Helen Chan	Hospital for Sick Children
Dr. Mary Corey	Hospital for Sick Children
Dr. John Dick	University of Toronto
Prof Bernard Dickens	Hospital for Sick Children
Dr. Peter Durie	Princess Margaret Hospital and HSC
Dr. Brenda Gallie	University of Toronto Faculty Association
Prof William Graham	Hospital for Sick Children
Dr. Christine Harrison	University of Toronto Faculty Association
Ms. Allison Hudgins	Sack, Goldblatt and Mitchell
Ms. Cathy Lace	University of Toronto Faculty Association
Prof Rhonda Love	McCarthy Tétrault / CMPA
Mr. Steven Mason	The Founders' Network, LIAR
Dr. Fraser Mustard	Harvard University
Dr. David Nathan	The Toronto Hospital and HSC
Dr. Nancy Olivieri	National Thalassemia Foundation
Polsinelli family	University of Toronto
Dr. Miriam Rossi	Hospital for Sick Children
Prof Mary Rowell	Queen's University
Prof D.A. Soberman	Canadian Association of University Teachers
Dr. James Turk	Oxford University
Prof Sir David Weatherall	

APPENDIX C

Persons Invited Who Did Not Participate in this Inquiry

Dr. Arnold Aberman*	The Toronto Hospital, University Health Network
Mr. A.R. Aird	Hospital for Sick Children
Dr. Gordana Atanackovic	Duchesnay, Incorporated
Dr. Matitiah Berkovitch	Assaf Harofeh Medical Centre
Dr. Robert Birgeneau	University of Toronto
Dr. Victor Blanche	Hospital for Sick Children
Dr. Manuel Buchwald	Hospital for Sick Children
Ms. Anne-Marie Christian	Hospital for Sick Children
Dr. Orna Diav-Citrin	Israeli Teratogen Information Service
Dr. John Evans*	Torstar Corporation
Dr. Alan Goldbloom	Hospital for Sick Children
Ms. Naomi Klein	Hospital for Sick Children
Dr. Gideon Koren	Hospital for Sick Children
Dr. Roderick McInnes	Hospital for Sick Children
Dr. Aideen Moore	Hospital for Sick Children
Dr. Heather Munroe-Blum	University of Toronto
Dr. David Naylor*	University of Toronto
Dr. Hugh O'Brodovich	Hospital for Sick Children
Mr. Brian Orr	Hospital for Sick Children
Mr. James Pitlabo	Hospital for Sick Children
Prof John Polanyi	University of Toronto
Prof Robert Prichard	University of Toronto
Prof Adel Sedra	University of Toronto
Dr. Barry Sherman	Apotex Incorporated
Dr. Louis Siminovitch	Mount Sinai Hospital
Dr. Peter Singer*	University of Toronto
Dr. Michael Spino	Apotex Incorporated
Mr. Michael Strofolino	Hospital for Sick Children
Dr. Cecil Yip	University of Toronto
Dr. Stanley Zlotkin	Hospital for Sick Children

**Provided written information to the inquiry on one or more topics*

Appendix D

Motions passed by CAUT at the request of the Committee of Inquiry

In order to ensure its independence, the Committee of Inquiry requested that the CAUT Executive Committee pass the following motions:

(i) 125th meeting of the CAUT Executive Committee, November 18, 1999.

O'NEIL/FIELD: WHEREAS the Olivieri case has already received extensive publicity, nationally and internationally,

WHEREAS reports of other inquiries into certain aspects of this case have been published in their entirety by the bodies that commissioned them;

THEREFORE be it resolved that the Executive Committee confirm that the Report of the Committee of Inquiry established by the Academic Freedom and Tenure Committee of CAUT into the Olivieri case will be published by the CAUT in its entirety as delivered and in a timely fashion, notwithstanding the discretion as to publication of reports provided for in the CAUT Policy Statement on Committees of Inquiry.

CARRIED UNANIMOUSLY

(ii) 126th meeting of the CAUT Executive Committee, January 11, 2000.

O'NEIL/BOOTH: THAT pursuant to the request from the Committee of Inquiry and the Academic Freedom and Tenure Committee,

1. provisions in the Policy Statement pertaining to a draft report be suspended for its inquiry;

2. the committee will be considered as a committee appointed by CAUT (not just by the AF&T committee), provided with terms of reference and resources by CAUT, but that the Committee operate fully independently. In order to ensure fairness, the Committee will follow the already agreed to Policy Statement on Committees of Inquiry except that: (A) There will be no draft report provided to CAUT, and (B) CAUT will publish the committee's final report as written and in a timely manner.

The committee will write to all contacts advising of the elimination of the draft stage, and the reason.

It is understood by the committee of inquiry that among the provisions of the Policy Statement remaining operative are those of paragraph 5, including, "The committee of inquiry shall, insofar as possible, give each party to the dispute against whom material adverse information has been received, a statement as to its content and the opportunity to rebut it."

The committee will seek legal advice on minimization of the risk of libel actions from Counsel Peter Jacobsen prior to submitting its report to CAUT for publication.

CARRIED UNANIMOUSLY

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Appendix E

Agreement among the University of Toronto, Dr. Nancy Olivieri and the Hospital for Sick Children, dated January 25, 1999; and letter by Sir David Weatherall and Dr. David Nathan recommending this agreement to the parties

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UNIVERSITY OF TORONTO
 27 King's College Circle, Simcoe Hall, Room 221
 Toronto, Ontario M5S 1A1, CANADA

January 25, 1999

Dr. Nancy Olivieri
 Department of Paediatrics
 Hospital for Sick Children
 555 University Avenue
 Toronto, ON
 M5G 1X8

Mr. Michael Strofolino
 President and CEO
 The Hospital of [sic] Sick Children
 555 University Avenue
 Toronto, ON
 M5G 1X8

Dear Dr. Olivieri and Mr. Strofolino:

We have had an opportunity to meet extensively with Dr. Olivieri and her counsel and with representatives of the HSC and their Counsel.

We believe that the attached letter from President Robert Pritchard of the University of Toronto containing a proposal for resolution of outstanding matters between the HSC and Dr. Olivieri represents a fair and balanced settlement of what has been a difficult and protracted dispute.

We are firmly of the view that the best interests of the HSC and of Dr. Olivieri and of medical science and research are served by agreeing to this proposal made by President Pritchard. We wholeheartedly and unreservedly recommend its acceptance by both parties.

Dated at the University of Toronto this 25th of January 1999

(Signed)

Professor Sir David Weatherall
 Regius Professor of Medicine
 John Radcliffe Hospital
 Oxford
 United Kingdom

(Signed)

Dr. David G. Nathan
 President
 Dana-Farber Cancer Institute
 Harvard Medical School
 Boston, MA

UNIVERSITY OF TORONTO

J. Robert S. Prichard,
President

January 25, 1999

Dr. Nancy Olivieri
Department of Paediatrics
Hospital for Sick Children
555 University Avenue
Toronto, ON
M5G 1X8

Mr. Michael Strofolino
President and CEO
The Hospital of [sic] Sick Children
555 University Avenue
Toronto, ON
M5G 1X8

Dear Nancy and Michael:

Reflecting our shared commitment to ensuring both that Nancy can continue her important work and that the Hospital for Sick Children can continue to advance its important mission, and in the interest of a comprehensive resolution of the matters that have divided you, I recommend a resolution on the following terms. In doing so I have been advised that Dr. Olivieri will retain her current appointment in the Toronto Hospital as the Director of the Haemoglobinopathy Program and Director of the Department of Medicine's Haemoglobinopathy Program.

1. Dr. Olivieri's primary appointment will shift from Paediatrics to Medicine: her cross-appointment will shift from Medicine to Paediatrics.
2. As soon as it is reasonably practicable, Dr. Olivieri will relocate her office to the Toronto Hospital (TH) from the Hospital for Sick Children (HSC).
3. Dr. Olivieri will remain on active staff at HSC in the Division of Haematology/Oncology. Dr. Olivieri will chair and lead the weekly Haemoglobinopathy Clinic meeting at HSC and have full access to and full responsibility and accountability for all haemoglobinopathy patients' medical care subject to ethical and HSC policies and practices. The previous position of Director of the Haemoglobinopathy Program at HSC will disappear with reorganization of the Division, and no similar position

will be created. Dr. Olivieri will remain a Senior Scientist in the Research Institute.

4. Dr. Olivieri will report to Dr. Michael Baker (Dr. MB) with respect to her HSC duties in his role as a member of the Department of Paediatrics in the Division of Haematology/Oncology and Dr. Baker will report to Dr. Victor Blanchette (Dr. VB).
5. HSC agrees that the resources and staffing of the clinic will be done in consultation with Dr. Baker and that the quality of care will remain at the highest level possible.
6. HSC and Dr. Olivieri agree to a clean slate and a new beginning and HSC agrees that all letters of discipline and complaint about Dr. Olivieri including the letter of January 6, 1999 from Drs. O'Brodovich and Blanchette will have continuing force or effect.
7. HSC and Dr. Olivieri and their lawyers agree not to initiate any legal actions against each other arising out of events before January 25, 1999.
8. If Dr. Olivieri is required to defend herself in any legal action brought by Apotex arising out of facts which occurred prior to January 25, 1999 for which CMPA refuses to provide coverage, HSC will pay her costs of defending such an action. In the unlikely events that Apotex were successful, HSC agrees to indemnify Dr. Olivieri with respect to any award or judgment.
9. HSC will indemnify Dr. Olivieri for actual legal and other expenses incurred to date to a maximum of \$150,000.
10. Dr. Olivieri will be granted a paid "mini-sabbatical" of six weeks as soon as Dr MB judges it to be possible and a paid sabbatical of twelve months at a mutually agreed time over the next three years pursuant to HSC/UT sabbatical policy.
11. Dr. Olivieri's compensation will not be negatively affected by this reorganization.
12. HSC agrees to continue to provide its current level of resources and staffing for the Haemoglobinopathy Program.
13. HSC agrees to withdraw any restriction on use of HSC's email or other forms of communication that might restrict, or appear to restrict, in any way the exercise of academic freedom by any member of the University faculty at HSC.
14. HSC agrees to withdraw letters of January 6, 1999 to Drs. Olivieri, Gallie, Durie and Chan reminding them of the Hospital's By-laws on communication with the media and not to pursue any alleged breach of these By-laws prior to January 25, 1999.

15. In order to facilitate the implementation of this agreement, Dean Aberman will provide an additional \$45,000 per year for two years to support appointment of a senior research PDF to work in Dr. Olivieri's programme and to give Dr. Olivieri sufficient lead time to apply for external grants to support this position beyond the two years.
16. If there are any disputes with respect to the implementation of this Agreement, HSC and Dr. Olivieri agree that the President of the University of Toronto will mediate such disputes.

Beyond the specifics of this recommended resolution, I want to record my understanding of your shared commitment to making all of this work. It will require effort and growing good will from everyone concerned. My colleagues and I in the senior administration of the University will be pleased to do all we can to contribute to your success.

As we have discussed, this resolution is without prejudice to grievances brought by the University of Toronto Faculty Association (UTFA) against the University on behalf of Dr. Olivieri and her colleagues and on behalf of the Association. These must be resolved between the University and UTFA through the grievance procedure.

I am very grateful to both of you and your colleagues for your willingness to embrace this resolution in the interest of moving forward together. Please indicate your consent to this resolution by signing this letter.

Warm regards,

J. Robert S. Prichard

(signed)

Dr. Nancy Olivieri

(signed)

Mr. Michael Stofolino

/rk

Appendix F

Legal Opinion by Professor Emeritus Daniel A. Soberman, Queen's University

Queen's University
Faculty of Law
Mar 21, 2000

Professor Jon Thompson, Chair, Committee of Inquiry

Re: Dr. Nancy Olivieri, Apotex Inc., Hospital for Sick Children
& University of Toronto

Dear Professor Thompson, [sic]

The following is a quote from the book of which I am a co-author*, in Chapter 5 on "Professional responsibility", under Informed Consent, at p. 99. At that page, we examine the duty to disclose, and in my opinion it clearly applies to a researcher participating in clinical trials in which patients are administered a study drug:

The setting of professional standards has a special application in the doctor-patient relationship. Many kinds of medical treatment involve risk-taking even when the procedure is carried out to the highest standards of care and skill; there may be a small chance that a patient will not respond well and will be worse off afterwards. The patient who has been harmed may complain that, had the risks been explained, he or she would never have submitted to the treatment; the doctor in failing to inform the patient fully of the risks did not obtain a proper consent. In effect, the treatment was not authorized.

...The courts have recognized a *patient's right to full information about the risks inherent in a treatment* and failure to inform fully normally amounts to negligence. When applying the principle, a court first considers whether the doctor disclosed every risk which he or she knew or ought to have known would be significant or material to the patient's decision to consent to the medical procedure. If the procedure is at the frontier of medical knowledge, and may, when performed, turn out unpredictably, the doctor must so inform the patient. However, the test applies only in relation to the standards and knowledge of the medical profession at the time the information is provided.

The court also considers a second question: would a reasonable person in the position of the patient, on a balance of probabilities, have decided against the procedure upon a proper disclosure of the risks? If the court is satisfied on the facts that the answer is "yes", then it is also saying that the failure to inform

*Smyth, Soberman, Easson, *The Law and Business Administration in Canada*. (8th ed.) Toronto: Prentice-Hall Canada Inc. 1998.

was not only a breach of duty but also caused the harm—and the patient will be awarded damages in compensation. [italics added]

I believe it is clear from the above discussion that a physician is under a legal duty to disclose “material” or “significant” risks, and that failure to do so may well amount to the tort of negligence.* The main issue of a physician’s liability may be whether the risk has any reasonable basis. At one extreme, if the “risk” were the result of some utterly unreasonable conclusion of a researcher—and no one else agreed that there was a risk—then non-disclosure would not amount to a breach of the duty of disclosure. (In such circumstances a clause prohibiting disclosure to the patient might still be lawful, because there would be no breach of duty towards the patient.)

However, if the researcher has a reasonable basis for her belief—for instance if one or more qualified and neutral researchers in the field agreed that there appeared to be a risk of harm to the patient by administering a particular treatment—then failure to disclose is a breach of her legal duty to that patient and committing a tort.

What then is the effect of a clause in a contract prohibiting disclosure to third parties? The “LA-01” contract, clause 7, states,

All information... obtained or generated by the investigators... shall be and remain secret and confidential and shall not be disclosed in any manner to any third party...

It seems clear that this clause is so broad and seeping in its wording that “in any manner to any third party” includes patients.

*To the extent that it prohibits a physician from disclosing to a patient information that the physician has acquired pursuant to her research (or otherwise), this clause is illegal and void if there is a material or significant risk to the patient.*** The patient must be given the opportunity to decide whether to proceed or continue with the treatment. In these circumstances, the researcher does not have to establish the complete accuracy of her concern—a risk is a risk, not a certainty—but only that it was not an unreasonable concern.

Accordingly, a central point in the Dr. Olivieri inquiry remains whether she had a reasonable basis for her concerns about the risks to patients in the study.

I hope these observations are helpful to you[.]

*There is a very large body of case law that developed in this area, in the 1980s and 1990s. Here are some of the leading cases: Reibl v. Hughes, [1980] 2 S.C.R. 880; Hopp v. Lepp, [1980] 2 S.C.R. 192; (both of the preceding cases were decisions of the Supreme court of Canada); Rawlings v. Lindsay (1982), 20 C.C.L.T. 301; Leung v. Campbell (1995), 24 C.C.L.T. (2d) 63.

A case of particular interest although older, creates an even higher standard for physicians participating in experimental studies on patients: Halusha v. University of Saskatchewan (1965), 53 D.L.R. (2d) 436.

**In my opinion, it is clear that any term in a contract that prohibits disclosure of information that would amount to the commission of a tort is, to the extent that it does so, illegal and void. (See p. 162, top of page, of our book. I have also attached pages from a leading textbook, Waddams, S.M., The Law of Contracts, (4th ed.) Toronto: Canada Law Book Inc., 1999.)

Yours sincerely,
(Signed)

Daniel A. Soberman
Emeritus Professor of Law

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Appendix G

Letters Received in Reply to Letters Sent 26 March 2001

THE HOSPITAL FOR SICK CHILDREN

March 30, 2001

Professor Jon Thompson,
Chair, Committee of Inquiry

Dear Professor Thompson:

RE: CAUT Committee of Inquiry

I am in receipt of your letter dated March 26, 2001 requesting information from the Board of Trustees in respect of the matters enumerated in your letter.

For the reasons outlined in our previous correspondence, I must respectfully decline your invitation.

Yours very truly,

(Signed)

Alexander R. Aird
Chairman
Board of Trustees

THE HOSPITAL FOR SICK CHILDREN /
UNIVERSITY OF TORONTO FACULTY OF MEDICINE

March 30, 2001

Dear Professor Thompson

Re: Committee of Inquiry into the case involving Dr. Nancy Olivieri, the
Hospital for Sick Children, the University of Toronto and Apotex Inc.

This is further to your letter of March 28, 2001. My position remains the same as
that set out in my letter to you of November 25, 1999. My reasons for taking that
position remain unchanged and need not be repeated. As a result, I intend to take
no part in the inquiry you refer to.

Sincerely yours,

(Signed)

Hugh O'Brodovich MD, FRCP (C)

Professor of Paediatrics and Physiology
Chairman of Paediatrics, University of Toronto
Paediatrician in Chief, Hospital for Sick Children
R.S. McLaughlin Foundation Chair in Pediatrics at The Hospital for Sick
Children

March 30, 2001

Dr. Jon Thompson Chair,
Committee of Inquiry

Dear Dr. Thompson:

Re: Committee of Inquiry into the case involving Dr. Nancy Olivieri, the
Hospital for Sick Children, the University of Toronto and Apotex Inc.

I write on behalf of Professor Love to answer the questions raised in your letter dated March 26, 2001.

To be clear, when CAUT contacted UTFA in late August 1998 to get background for an article that was being published in the September CAUT Bulletin on the matter, I phoned the former president of the Faculty Association, Professor Cecil Yip, as a faculty member with whom I had prior dealings. I knew Professor Yip was in Medicine and would be knowledgeable regarding University research policy. I had not kept track of Professor Yip's career and did not realize that at the time he was in fact the Vice-Dean Research in the Faculty of Medicine and therefore directly implicated in the case. When I phoned Professor Yip just before August 26, 2001 in response to Jim Turk's question regarding what U of T policies were at issue, the response was very much framed as being a Hospital for Sick Children case unconnected to the University—something that never would happen at the University. Moreover, I don't recall Cecil alerting me to his new position or to his involvement in the case. From my perspective, I was getting information for a CAUT newspaper story and the people involved were not members of our Association.

UTFA is unusual in that it is a voluntary association with an agreement outside the Labour Relations Act. As such, we do not automatically owe the same duty to represent nonmembers that most Associations do under the Labour Relations Act. Indeed, individuals are free to hire their own lawyers to represent them in their grievances and dealings with the University absent the Faculty Association.

Moreover, UTFA had one of, if not the highest, grievance caseload in the country at this time and whereas CAUT had been available in the past to assist with overload cases, CAUT was in the process of reorganizing the provision of its legal services and UTFA was no longer able to get overload legal service support from CAUT. In short, UTFA, in the opinion of its General Counsel, was barely managing to handle the caseload it had without creating liability for its members. The idea that we would or could go out and try to get non-members to join so that we could take on their case would have been a break with traditional practice.

Dr. Olivieri called UTFA after August 26, 1998, perhaps in early September. Professor Love spoke to her. Professor Love told her, that even though she and her colleagues were not members of UTFA, she would be happy to meet with them. She never called Professor Love again. That is in Professor Love's view of

why, as you say, “no action was taken by the UTFA in the late summer of 1998, and for two more months.” You state that “the question arises as to whether the UTFA considers that it has a positive duty to contact a professor whose academic freedom may be in jeopardy....” That is a good question. UTFA has more grievances than any other Association in Canada, and we don’t look for work from non-members. However, just recently, UTFA did phone someone who has been a member for a long time when UTFA heard of academic freedom troubles.

Professor Love and I met with the Vice-Provost Paul Gooch and Provost Adel Sedra on August 26, 1998 from 9:30 a.m. to 11:30 a.m. We were phoned by them to meet the same day that I had phoned Cecil Yip. Indeed, Professor Love and I were told that NO University policies had been violated and that the entire matter was internal to the Hospital.

Professor Dyck phoned the UTFA office on the day that Bill Graham (then UTFA President) was leaving to go to Ottawa for a CAUT Executive/Council meeting in November 1998. Professor Love told the UTFA Secretary that Professor Love would speak to Professor Dyck if he wanted. But, it seemed he wanted to speak only to Bill Graham. The secretary gave Graham’s Ottawa phone number to Dyck and UTFA did not hear anymore for a few days while CAUT considered what it would do.

After that CAUT meeting, UTFA met with the grievors and began a lengthy process of hearing their story, meeting with the Grievance Committee, the Executive and the Council. As we knew the case would be complicated, we wanted to follow a careful process of recommending to Council that they become members.

So the answer to “...whether the UTFA considers that it has a positive duty to contact a professor whose academic freedom may be in jeopardy, in circumstances where the UTFA has information on the case...” is not where the professor is not a member of the Association and the Association has no duty to represent that professor.

That answer must be qualified with the knowledge that UTFA recognizes the interests of its members would be better served if it had the resources to act in such a proactive manner, but the hard reality is that emerging from the Social Contract, members salaries had witnessed very small increases and the revenues of the Association, being a direct percentage of those salaries, had similarly been constrained. There was virtually no local political support, understandably, in such a climate for dues increases, despite the skyrocketing demand for legal services that arose out of the very same inimical economic environment.

As for your second question, regarding the “opportunity for the UTFA and the CAUT to make representations to the Hospital, perhaps jointly with the University, to request that Dr. Olivieri be provided with due process in the MAC proceedings” you are correct in observing that UTFA did not take this opportunity. The January agreement had specifically provided a mechanism for paying for Nancy’s personal lawyer, Beth Symes, to make representation to the MAC on those very issues and UTFA extensively supported and assisted Ms.

Symes in that work, including the General Counsel personally assisting in the review and editing of the original MAC submissions, but UTFA did not separately make representations to the MAC.

As above, the expense of litigating the complex and interconnected series of cases was ever present in the minds of the officers of the Association and the fact that Dr. Olivieri's personal lawyer was looking after the Hospital qua Hospital was deemed sufficient. The Association's job was to utilize the grievance procedure to meet the client's objectives and to deal with University processes. It was not in any sense clear that UTFA would be granted standing before the MAC and the scarce resources had to be applied to areas where no representation was being made. In early 1999, the Association was advised by its external counsel that progress would not likely be made under the existing Grievance Review Panel and a strategic decision was made to wait until the appointment of a new Chair of the Panel in July 1999. At the time, we had no idea that it would take six months to agree on a Chair, up to and including threatening to bring a judicial review to mandamus an appropriate appointment, and a further 9 months to ensure the legal advisor to the Panel had no conflict of interest.

I might frankly admit that there were institutional problems that exacerbated our response. Around September 15 or so, 1998, I went on maternity leave. Given relatively few number of clinicians whose grievances we were handling at the time (we had opened two clinical faculty files in the preceding year) and the problematic nature of UTFA's internal information systems, the fact that clinical faculty members had been represented since 1975 appeared to get a bit lost. Moreover, our external counsel, when consulted, advised us to put through certain changes in our constitution to deal with clinical faculty as members. These changes were unnecessary in my view since we had represented clinicians since 1975 without such amendments. However, there was a need to establish a policy to deal with dues deductions where faculty members did not have university pay directly and that was dealt with by the amendments.

At any rate, those machinations slowed considerably UTFA's involvement, in part because we do not act for non-members as a rule. Moreover, it reinforced the erroneous impression that the Hospital was truly separate and apart from the University, an impression that would only completely be put to rest in early 2000, when Ms. Symes and Mr. Ruby were removed from representing Dr. Olivieri and her colleagues. [sic] Ms. Symes had always been of the view that the Hospital was a separate entity and less clear of its interrelationship with the University. Our grievors seemed to be similarly misinformed and it took some time to tease out the complex interrelationships amid the seemingly daily harassment and proceedings. In early 2000, UTFA's external counsel took over the Hospital related representation of Dr. Olivieri (i.e. MAC proceedings) in addition to assisting us. With time, closer examination of the documents made it clear that the original impression of separation was a strategic, illusory and erroneous ploy of the administration. Moreover, with the same counsel representing her at both institution, a more interrelated representation became

possible. However, duplication of legal expenses still argued against UTFA making its own representations and the Hospital soon took the matter out of UTFA's hands by divesting itself of the MAC issue to the University and the College of Physicians and Surgeons simultaneously on April 17, 2000 in a national press conference.

Moreover, the monetary constraints meant that the case was never handed out completely to our external lawyer's, [sic] despite a consensus among the legal staff that that would have been the appropriate route to go. When I gave notice of quitting in December 1999, the external lawyers became more involved and even then the external lawyers were reluctant at that point to solely take on the case given its enormity and the refore con comittant [sic] cost.

I hope this addresses your questions. If you require any further clarification, please feel free to contact either me or Professor Love.

Yours very truly,

(Signed)

Allison Hudgins
Senior Counsel

THE HOSPITAL FOR SICK CHILDREN

April 2, 2001

Professor Jon Thompson
Chair, Committee of Inquiry

Dear Professor Thompson:

Re: Committee of Inquiry into the case involving Dr. Nancy Olivieri, the
Hospital for Sick Children

This will acknowledge your letter of March 26, 2001.

The position outlined in my letter of November 26, 1999 together with my
reason for taking that position remain unchanged. Accordingly, I intend to take
no part in the Inquiry you refer to.

Yours truly,

(Signed)

Manuel Buchwald, O.C., PH. D, F.R.S.C.

HSC Chief of Research, Director of the Research Institute

THE HOSPITAL FOR SICK CHILDREN
April 6, 2001

Professor Jon Thompson
Chair, Committee of Inquiry

Dear Professor Thompson:

Re: CAUT Committee of Inquiry

I have received your letter of March 28, 2001. I am declining your invitation for the same reasons that have been set out by Mr. Aird in his correspondence with you.

Yours truly,
(Signed)
L.E. Becker, MD FRCPC

ARNIE ABERMAN

April 18, 2001

Dr. Jon Thompson
Chair, CAUT Committee of Inquiry

Dear Jon:

Re: CAUT Committee of Inquiry into case involving Dr. Nancy Olivieri, the
Hospital for Sick Children, the University of Toronto and Apotex Inc.

I am responding to your letter of March 26, 2001.

I advised you more than a year ago that, notwithstanding the obvious problems with the composition of the CAUT Committee of Inquiry (Committee) and with the Committee's procedures, I was willing to review any information that the Committee received about me. I had not heard from the Committee until I received your letter of March 26, 2001. As you know, CAUT policy required you to send me any materially adverse information "reasonably in advance" of the publication of your report, presumably to provide me with an opportunity to correct the record. I was therefore surprised to read in the letter that the Committee had begun to write the report before I even saw, let alone commented on, the information received about me.

The information about me in your letter is incomplete, incorrect, and misleading and is more accurately characterized as misinformation. I have documentation (e-mails and letters) that completes, corrects, and clarifies that misinformation. I want to help the Committee write an accurate report (at least where it involves me) so, as you requested, I am willing to make that documentation, as well as testimony about that documentation, available to the Committee. However, I may need the Committee's assistance before I can do so. Let me explain why.

As you know, UTFA (a member of CAUT) has filed grievances—all of which, in my view, have no merit—on behalf of Professor Nancy Olivieri and others against me and other former and current senior academic administrators of the University of Toronto on the very same case that is before the Committee. We are now in the midst of these grievance procedures (UTFA Newsbulletin #2—February 22, 2001) before the Grievance Review Panel (Panel).

One of UTFA's grievances against me is that I released and made available, without her consent, Professor Olivieri's private e-mail correspondence to her colleagues in academic institutions, thereby violating, in UTFA's view, the UTFA/UofT Memorandum of Agreement (Memorandum). The documentation referred to in the third paragraph above, and which I have also been asked to

produce to the Panel (for the purposes of the grievance procedure and for no other purpose), includes e-mails and letters to, from, and about the following sixteen faculty colleagues—Manuel Buchwald, Helen Chan, Padraig Darby, John Dick, Peter Durie, Marty Friedland, Brenda Gallie, Alan Goldbloom, Gidi Koren, Nancy Krieger, Hugh Obrodovich [sic], Nancy Olivieri, Bob Phillips, Paul Ranalli, Adel Sedra, and Graham Sher. Therefore, unless I get the consent of these faculty colleagues to the release of these e-mails to the Committee, I cannot make the material available to you without further violating, in UTFA's view, the Memorandum. Note the bind that CAUT has put me in. At the same time that its Committee of Inquiry threatens to print falsehoods about me unless I release certain e-mails, CAUT's member UTFA says that releasing these e-mails without consent is a grievable offense.

To make matters more perverse, UTFA objects to investigations outside of those specified by the Memorandum (UTFA Press Release—February 21, 2001, and UTFA Press Release—March 7, 2001). UTFA considers such investigations—which I assume would include the CAUT Committee of Inquiry—as indicating a lack of respect for due process and grounds for a grievance. Therefore, as a former senior member of the University of Toronto's academic administration, it seems that, according to UTFA, I cannot even participate in the Committee's work without creating a grievable act.

For these reasons, I am writing to ask the CAUT Committee of Inquiry to obtain a commitment from UTFA, a member of CAUT, not to grieve my participation in the Committee's work; to obtain consent by the sixteen faculty colleagues mentioned above to the release of their e-mail and letters; and to obtain consent by the Panel to the release of this documentation. I am willing to help the Committee obtain the consent of my faculty colleagues and of the Panel. (Presumably, you will not need my assistance to obtain the commitment from UTFA.) If we are unable to obtain such an UTFA commitment and these consents, it would be inappropriate and disrespectful of grievance review procedures—and, according to UTFA, in violation of the Memorandum, and hence grievable—for me to participate in the Committee's work or to make available directly to the Committee the very same material I will provide to the Panel and the involved parties in the context of the grievance proceedings.

If we are unable to obtain the necessary commitment and consents, I suggest the following approach. I will ensure that my presentation to the Panel, during the grievance hearings, addresses and rectifies the incomplete, incorrect and misleading material about me contained in your letter of March 26, 2001. You are welcome to attend these hearings since they are open to the public. During the grievance hearings, UTFA will have an opportunity both to review any documentary material I release to the Panel and to ask questions to me on my testimony. I will not object if the Committee, either directly or through UTFA's lawyers, wishes further clarification on my testimony. This accomplishes what you requested me to do in your letter of March 26, 2001—namely to comment on the misinformation in that letter and to produce relevant information, but in

circumstances where UTFA, a unit of CAUT which created the Committee, does not consider the Memorandum is being violated and where I am not being disrespectful of the grievance review procedures.

Please advise me whether you are able to get the necessary commitment and consents or whether you prefer that I respond to your letter of March 26, 2001, during my presentation to the Panel.

I have now advised you that the material about me in your letter of April 26, 2001, is incomplete, incorrect, and misleading, and I have laid out a clear path for you to obtain the complete and correct facts from me. Therefore, if you issue a report without my input, it would be in reckless disregard for the truth and would demonstrate a malicious intent to damage my reputation. If you do issue such a report, please indicate in the body of the report that I consider the information about me to be incomplete, incorrect and misleading and include a copy of this letter as an appendix to the report, so that readers will be provided with the reasons why I was unable to participate in your inquiry.

Finally, do not misinterpret this letter as my consent to CAUT or the Committee to receive, distribute or publish material about me that is incorrect, incomplete or misleading. You have no such consent and I will take all necessary steps to protect my reputation.

Sincerely,
(Signed)
Arnie Aberman
Professor of Medicine
University of Toronto

- c. Dr. Jocelyn Downie (unsigned version only sent by e-mail attachment)
Dr. Patricia Baird (unsigned version only send by e-mail attachment)

THE ISRAELI TARATOGEN INFORMATION SERVICE

April 20th 2001

Dr. Jon Thompson
Chair, Committee of Inquiry

Dear Dr. Jon Thompson

Re: Committee of Inquiry into the case involving Dr. Nancy Olivieri, the
Hospital for Sick Children, the University of Toronto and Apotex Inc.

1. Aspects a) to h) should be addressed to the corresponding author of the article, Dr. G. Koren.
2. The Research Institute of the Hospital for Sick Children conducted an investigation in regard to the incident in the thalassemia clinic. I gave full details to the committee headed by Dr. Manuel Buchwald. For further information you may contact them.

Truly,
(Signed)
Dr. Orna Diav-Citrin

DUCHESNAY

April 27, 2001

Dr. John [sic] Thompson
Chair, Committee of Inquiry

Dear Dr. Thompson:

RE: Committee of Inquiry into the case involving Dr. Nancy Olivieri, the
Hospital for Sick Children, the University of Toronto and Apotex Inc.

I am writing to you in response to the letter of March 26, 2001 re inquiry you
have asked:

1. I believe that you can get all information you need from the Medical Advisory
Committee of the Hospital for Sick Children. As you know, patients' data are
strictly confidential, kept in the health record and in this case, due to study
participation, in the Case report forms that were submitted to Apotex Inc.
2. I believe that all the answers [sic] have already been provided to the Dean of
the Medical School, University of Toronto, Dr. Naylor. If you have any further
questions, please refer them to the senior and corresponding author of the article,
Dr. Koren.

Sincerely,
(Signed)

Dr. Gordana Atanackovic
Medical Research Director
Duchesnay Inc.

April 28, 2001

Dr. Jon Thompson
Chair, Committee of Inquiry

Dear Dr. Thompson:

I am in receipt of your letter of March 26, 2001.

The C.A.U.T. is a notorious and strong supporter of Dr. Olivieri. It is also directly linked to U.T.F.A., which has repeatedly called for the termination of my appointment at the University of Toronto. Your Committee lacks any real, let alone apparent, independence, impartiality or objectivity. I will not participate in your so-called inquiry.

Given the C.A.U.T.'s clear bias, it is not surprising to see that your letter contains several false and malicious statements about me.

Your letter also refers to a number of documents and events which are confidential and protected by long-standing university policy. Your Committee must be aware that it should not have such documents nor should it have been told of such events by others and, further, it must know that these breaches of confidence are violations of university policies and the Memorandum of Agreement.

If you publish untrue statements about me or breach my right to confidence, I will take appropriate proceedings against the members of your Committee and the C.A.U.T.

Yours truly,
(Signed)

Gideon Koren, D, FACMT, FRCPC
Director, The Motherisk Program
Professor of Pediatrics, Pharmacology, Pharmacy, Medicine and Medical
Genetics
The University of Toronto
Senior Scientist, The Research Institute
The Hospital for Sick Children, Canada

Cc: Mr. Eddy Greenspan
Mr. Mark Adilman
Dean David Naylor
Dr. Hugh O'Brodovich
Mr. Angus McKinnon

CAUT / ACPPU

April 30, 2001

Dr. Jon Thompson, Chair, Committee of Inquiry

Dear Dr. Thompson:

I am replying to your letter of March 26, 2001, regarding CAUT actions in respect to Dr. Nancy Olivieri. You make two points, and I would like to comment on each.

1. The failure of CAUT to act in a more expeditious manner

You are correct in noting that CAUT did not act on the case until November, 1998, even though we wrote about it in the September 1998 issue of the *CAUT Bulletin*. At that time, CAUT waited until cases were brought to our attention by a member faculty association and then we referred the matter to our Academic Freedom and Tenure Committee, which meets quarterly. While the Olivieri case was in the news for some time prior to the fall of 1998, CAUT had not received a request to intervene. When it was brought to our attention, we did forward it to our Academic Freedom and Tenure Committee and “speeded up” the process by putting a lead article in the *Bulletin*.

As you suggest, there are serious flaws in this approach, and we are now revising how we deal with such serious and urgent cases.

2. CAUT's failure to intervene [sic] the MAC's investigation of Dr. Olivieri

During this period, CAUT was working with the University of Toronto Faculty Association (UTFA) on the Olivieri case. UTFA took the lead on [sic] dealing with the Hospital for Sick Children's Medical Advisory Committee (MAC) investigation. You are correct in noting that CAUT could have intervened in this matter more directly.

While both of your criticisms are justified, I must note that CAUT played an active role in late 1998 and early 1999 in helping bring about the January 1999 “initial settlement” in which Dr. Olivieri regained her responsibility for all haemoglobinopathy patients at the Hospital for Sick Children (HSC) and at the Toronto Hospital, had all letters of discipline and complaint against her deemed of no effect, received assurance that the HSC would pay her legal costs if she were sued by Apotex, was to be reimbursed by HSC for up to \$150,000 for legal costs incurred to date, and was to be provided \$45,000 a year for two years by the University to support a senior researcher in her program.

Yours sincerely,

(Signed)

Thomas Booth, President

HEENAN BLA IKIE

May 18, 2001

Dr. Jon Thompson
Chair, Committee of Inquiry

Dear Dr. Thompson:

Re: Committee of Inquiry into the case involving Dr. Nancy Olivieri, the
Hospital for Sick Children, the University of Toronto and Apotex Inc.

I act for various members past and present of the administration of the
University of Toronto. I am instructed to advise you and other members of the
CAUT Committee of Inquiry inquiring into the cases [sic] involving Dr. Nancy
Olivieri, the Hospital for Sick Children and the University of Toronto, that
should the Committee publish statements which are defamatory to my clients,
they will not hesitate to initiate legal proceedings against the individual members
of the Committee and CAUT.

Yours very truly,
(Signed)
John C. Murray

JCM/kd

CONFIDENTIAL

June 15, 2001

Dr. Arnold Aberman

Dear Arnie:

Re: Committee of Inquiry into case involving Dr. Nancy Olivieri, the Hospital for Sick Children, the University of Toronto and Apotex Inc.

I am responding to your letter of April 18, 2001, sent in reply to my letter of March 26, 2001. As you requested, a copy of this letter is being sent to you by fax.

As you noted, I provided information to you "reasonably in advance" of the publication of our report and invited you to respond by April 30, 2001 with relevant information. In reply you characterized the information I provided as "misinformation," but gave no details in support of this characterization. Instead you outlined conditions under which you suggested our inquiry could obtain further information. Your suggestions appear to be based on misunderstandings regarding our inquiry and regarding grievance proceedings.

Dr. Baird, Dr. Downie and I agreed to undertake this inquiry because we believe that matters important to the public interest are involved, and only on condition we would be independent of CAUT, or any other organization or person. It would materially restrict our independence if we were to agree to make the completion of our work contingent on events in a grievance proceeding, or contingent on the agreement of individuals or organizations regarding access to information. Thus we cannot reasonably be expected to accept your conditions.

In addition, and quite aside from the matter of independence, there is the practical matter that in any given grievance proceeding little or no information may be made available, since, for example, the parties could agree to settle the specific issues of the proceeding before any or all witnesses are heard. Alternatively, a proceeding could extend over a very long time. Your proposal offers no assurance that the information you say you have would be made available to us.

Your letter says that CAUT, UTFA and our inquiry have put you in a "bind." This is not correct. UTFA is autonomous with respect to administration of its agreement on terms and conditions of employment with its university. UTFA has been participating in this inquiry and has been open about its participation. It is therefore hard to believe that UTFA would attempt to impede you, or anyone else, from participating. You could raise your concern directly with UTFA before sending us documentation, if you are in doubt.

We believe that our inquiry procedures are reasonable. Early in our inquiry we invited you to participate. You did not accept, and in communications with me in late 1999 cited grievances by UTFA among your reasons. Pursuant to our procedures, I wrote to you in March 2001 and invited a response to information we had received. In reply you outlined conditions we cannot accept, for the reasons noted above. We also cannot accept your allegation that publishing a report on important matters of public interest based on a reasonable inquiry process can fairly be characterized as “reckless” or “malicious.”

If on receipt of this letter, you decide to provide information, we shall be pleased to give it due consideration if we receive it before June 30, 2001.

Sincerely,

(Signed)

Jon Thompson Chair, Committee of Inquiry

cc. Dr. Patricia Baird and Dr. Jocelyn Downie

ARNIE ABERMAN

June 22, 2001

Dr. Jon Thompson Chair,
CAUT Committee of Inquiry

Dear Jon:

Re: CAUT Committee of Inquiry into case involving Dr. Nancy Olivieri the
Hospital for Sick Children the University of Toronto and Apotex Inc.

I am responding to your letter of June 15, 2001.

I am disappointed that the CAUT Committee of Inquiry appears to be determined to publish a report, without my input, containing, according to your letter of March 26, 2001, conclusions about me that are incomplete, incorrect and/or misleading. You are unwilling to take the reasonable steps that I outlined in my letter of April 18, 2001, that will allow me to correct that misinformation without violating, in the opinion of UFTA (a unit of CAUT that created the Committee), the UTFA/UofT Memorandum of Agreement and without being disrespectful of UofT grievance review procedures.

As you know, the incomplete, incorrect and misleading conclusions are regarding the very same allegations that are the subject of grievances against other current and former senior UofT academic administrators and me. These grievances, brought by UTFA, are currently before a Grievance Review Panel at the UofT. The procedures of the Grievance Review Panel allow me to see the documents that form the basis of the allegations so that I can respond appropriately. In contrast, your letter of March 26, 2001, contained conclusions about me, but the documents that form the basis of those conclusions were not included. Not allowing me to review the documents that led you to your conclusions about me is hardly a “reasonable” procedure and is not in keeping with the essential components of fairness. The testimony and evidence that I will produce during the grievance procedures will show that these allegations have no merit and thus your report—if you proceed on the basis that you threaten to in your letter of June 15, 2001—will be incomplete, incorrect, and misleading, at least where it refers to me.

Let me give one example of the incomplete, incorrect and misleading information of your letter of March 26, 2001. I can do this because unlike the other misinformation, this example will not require producing emails and letters to and from other faculty members without their consent—consent you are not willing to obtain, even with my assistance.

In your letter of March 26, 2001, you apparently object (apparently, because your letter is obtuse) to my characterizing the report of the Investigating Committee (formed under the Faculty of Medicine’s Framework for Ethical Conduct of Research and Guidelines to Address Research Misconduct) that reviewed Dr. Olivieri’s complaint against Dr. Sher, as providing “full exoneration” to Dr. Graham Sher, in my letter to Dr. Sher which I copied to others.

You appear not to be not aware that the Framework document, publicly available at the Faculty of Medicine's Website ([http://www.library.utoronto.ca/medicine/student and staff/reg framework.html](http://www.library.utoronto.ca/medicine/student%20and%20staff/reg%20framework.html)), has the following procedure under Section 5.2 of "Disposition of Investigation".

"5.2 When an investigation determines that no fraud, misconduct or serious scientific error was committed, the Dean shall ensure that a letter confirming full exoneration is sent to the accused, with a copy to the complainant and to all other persons with knowledge of the accusation."

In your letter of March 26, 2001, you acknowledge that the report of the Investigating Committee specifically concluded that "that no fraud, misconduct or serious scientific error was committed by Dr. Sher". Therefore, the letter to Dr. Sher, that was copied to the complainant and others, and that used the words "full exoneration", was explicitly required by UofT policy. I assure you that the other conclusions about me are equally incomplete, equally incorrect and equally misleading, and I will respectfully demonstrate so to the Grievance Review Panel citing equally unequivocal evidence.

I urge you to reconsider your decision to proceed with the report without waiting for the Grievance Review Panel to complete its work. To go ahead now will indelibly brand the report as simply part of UTFA's grievance pleadings.

If you do proceed with publishing the report, I request the following. Where, in the report, you make the allegations or draw the conclusions about me contained in your letter of March 26, 2001, note that I consider these allegations and conclusions incomplete, incorrect and misleading. In addition, include my letter of April 18, 2001 and this letter in the appendix to the report and also, to provide context, your letters to me of March 26, 2001, and June 15, 2001.

Finally, do not misinterpret this letter as my consent to CAUT or the Committee to receive, distribute or publish material about me that is incorrect, incomplete or misleading. You have no such consent and I will take all necessary steps to protect my reputation.

Sincerely,

Arnie Aberman
Professor of Medicine University of Toronto

- c. Dr. Jocelyn Downie (unsigned version only sent by e-mail attachment)
- Dr. Patricia Baird (unsigned version only send by e-mail attachment)

Appendix H

Documentary Archive of the Committee of Inquiry

The Canadian Association of University Teachers has agreed to maintain an archive of the documents of the Committee of Inquiry.

To ensure independence of the inquiry and its report, arrangements were made to transfer the documents to CAUT after publication of the report.

Appendix I

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