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**Supplement to the 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.**

by

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The purpose of this Supplement is to discuss decisions by three independent bodies issued after the Report of the Committee of Inquiry was published on October 26, 2001, and a Commentary on the Report of the Committee of Inquiry published in December 2001.

### **A. Background**

The dispute between Dr. Nancy Olivieri and Apotex Inc. began in 1996, when Apotex attempted to deter her from informing patients and others of a treatment risk she had identified in a trial the company sponsored. Dr. Olivieri, a specialist in hematology and internal medicine, is a Professor of Pediatrics and Medicine in the University of Toronto, and a staff physician in the Hospital for Sick Children (HSC). She had been conducting clinical trials of Apotex's iron-chelation drug deferiprone (L1) with two groups of transfusion-dependent thalassemia patients, when the unexpected risk was identified. Apotex terminated the clinical trials and issued warnings of legal action should Dr. Olivieri inform patients or others of the risk. The resulting controversy widened and became public two years later, when many HSC scientists and physicians raised concerns that neither the Hospital, nor the University, had provided effective support for the ethical principles at stake or for Dr. Olivieri's rights against actions by Apotex.

In September 1998, with adverse publicity continuing, the Hospital's Board of Trustees agreed to demands for an external review of the facts and circumstances giving rise to the controversy. The Board unilaterally contracted with Dr. Arnold Naimark to conduct the review and asked him to report within three months. Two months later, Dr. Naimark engaged Drs. Bartha Knoppers and Frederick Lowy to assist him in completing his

review. Dr. Olivieri decided not participate in this Review as the conditions of a negotiated agreement for her participation were not met. Dr. Naimark's report, "Clinical Trials of L1 (Deferiprone) at The Hospital for Sick Children – A Review of Facts and Circumstances" (hereinafter the "Naimark Report"), said that Dr. Olivieri had failed in a purported obligation to report a second unexpected risk of the drug L1 to the Hospital's Research Ethics Board (REB) in a timely fashion. She had identified this risk during the non-trial Emergency Drug Release (EDR) L1 treatment period that followed Apotex's termination of both Toronto L1 trials. Dr. Olivieri disputed this finding in the Naimark Report, noting that the patients were not under REB jurisdiction during this period, and that she had in fact informed the patients and all others she was obligated to inform.

The controversy intensified when, on December 9, 1998, the same day it released the Naimark Report, the HSC Board of Trustees referred questions about Dr. Olivieri's conduct to the Hospital's disciplinary body, the Medical Advisory Committee (MAC). The MAC then received allegations against Dr. Olivieri which were not disclosed to her. The allegations were put forward principally by Dr. Gideon Koren, who had been Dr. Olivieri's co-investigator in the L1 trials, together with Dr. Hugh O'Brodovich, HSC's Pediatrician-in-Chief. The allegations were believed by the MAC and the Board, and in April 2000, HSC in a press conference referred the MAC's allegations against Dr. Olivieri to the Complaints Committee of the College of Physicians and Surgeons of Ontario (CPSO), and to the University's Faculty of Medicine.

During the period of the Naimark Review and the subsequent MAC investigation, Dr. Koren made a series of efforts to discredit Dr. Olivieri: in testimony to the Naimark Review; in testimony to the MAC; and in a series of anonymous letters to the press and others directed against Dr. Olivieri and three of her supporters, Drs. Helen Chan, Peter Durie and Brenda Gallie. After Drs. Chan, Durie, Gallie and Olivieri lodged complaints against Dr. Koren with the Hospital and the University about the anonymous letters, Dr. Koren lied persistently to conceal his actions as author of the letters. He later admitted responsibility, but only after Drs. Chan, Durie, Gallie and Olivieri obtained DNA evidence identifying him as the author. Drs. Chan, Durie, Gallie lodged complaints against Dr. Koren with the CPSO Complaints Committee.

As the dispute continued to escalate in 1999, the Canadian Association of University Teachers (CAUT) established a Committee of Inquiry, whose members were Drs. Patricia Baird, Jocelyn Downie and Jon Thompson (Chair). The members agreed to serve provided measures were implemented to ensure their independence, and they served without remuneration.

On October 26, 2001, following the completion of a two-year investigation, the Report of the Committee of Inquiry was published.<sup>1</sup> The Report exonerated Dr. Olivieri and faulted the University and the Hospital for not providing effective support for the principles at stake or for Dr. Olivieri's rights. The Report faulted Apotex for its attempts to prevent disclosure of information on risks of L1. The Report faulted Apotex also for its attempts to discredit Dr. Olivieri in its efforts to obtain regulatory approval to market L1. The Report faulted Dr. Koren for dishonesty in attempts to discredit Dr. Olivieri, and

for scientific misconduct in connection with his publication of findings on L1. The Report faulted CAUT and the University of Toronto Faculty Association for not intervening in the case until three months after they first learned of it. In addition, the Committee's Report criticized the Naimark Report on a number of grounds, and criticized the MAC and the HSC Board for the unfairness of the MAC process.

## **B. Purpose of this Supplement**

During the three months following the publication of the Report of the Committee of Inquiry, three independent bodies issued decisions, each relating to some of the subject matter of the Report of the Committee of Inquiry. Each of these three decisions confirms the findings in the Report of the Committee of Inquiry on the matters discussed in common. In addition, a Commentary on the Report of the Committee of Inquiry was published by the authors of the Naimark Report. The purpose of this Supplement is to discuss these four documents. The three decision documents are:

- The Report (with decision and reasons) of the Health Professions Appeal and Review Board of Ontario concerning a complaint against Dr. Gideon Koren filed with the Complaints Committee of the CPSO by Drs. Helen Chan, Peter Durie and Brenda Gallie. The Report of the Appeal and Review Board is dated October 11, 2001, but was issued to the parties on or about October 26, 2001. It did not become public until it was the subject of a newspaper article on November 22, 2001.<sup>2</sup> (This will be referred to as "Appeal Board Report.")
- The Report (with decision and reasons) issued December 19, 2001 by the Complaints Committee of the College of Physicians and Surgeons of Ontario (CPSO) on the allegations lodged by the Hospital for Sick Children (HSC) against Dr. Nancy Olivieri with CPSO.<sup>3</sup> (This will be referred to as "Complaints Committee Report.")
- A written decision issued January 7, 2002 by Dr. David Naylor, Dean of the Faculty of Medicine and Vice Provost for Relations with Health Care Institutions of the University of Toronto, on the allegations lodged by HSC against Dr. Olivieri with the University.<sup>4</sup> (This will be referred to as "Dean's Decision.")

The Commentary is:

- "Commentary - On selected aspects of the Report of the Canadian Association of University Teachers Committee of Inquiry on the Case of Dr. Nancy Olivieri, the Hospital for Sick Children, the University of Toronto and Apotex Inc.," by the authors of the Naimark Report, the Reviewer Dr. Arnold Naimark and his two Associate Reviewers, Drs. Bartha Maria Knoppers and Frederick H. Lowy. It is dated "December 2001" and is posted on the HSC website.<sup>5</sup> (This will be referred to as "Naimark Commentary.")

The following additional abbreviations are used:

“Naimark Report” = Report titled “Clinical Trials of L1 (Deferiprone) at The Hospital for Sick Children – A Review of Facts and Circumstances,” published December 9, 1998

“Inquiry Report” = “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.,” published October 26, 2001

In this Supplement, since the Dean’s Decision to dismiss the allegations against Dr. Olivieri was contingent on and followed the decision of the CPSO Complaints Committee, we mainly discuss the other three of the four recently issued documents: the Appeal Board Report on Dr. Koren, the Complaints Committee Report on Dr. Olivieri, and the Naimark Commentary on the Inquiry Report.

**C. The Report (with decision and reasons) of the Health Professions Appeal and Review Board of Ontario concerning a complaint against Dr. Gideon Koren filed with the Complaints Committee of the CPSO by Drs. Helen Chan, Peter Durie and Brenda Gallie [Appeal Board Report]**

Drs. Chan, Durie and Gallie lodged complaints against Dr. Koren regarding the anonymous letters and other matters with the CPSO Complaints Committee. The Complaints Committee found Dr. Koren’s conduct in the matter of the anonymous letters unprofessional and required that he attend at CPSO “to be cautioned,” but held that “it would not serve the best interest of either the public or the profession to refer this matter [Dr. Koren’s conduct] to the [CPSO] Discipline Committee.”<sup>6</sup> In reaching this decision, the Complaints Committee cited, among other things, the fact that Dr. Koren had already been disciplined by HSC.\*

Drs. Chan, Durie and Gallie considered this decision to be inappropriate and appealed it to the Health Professions Appeal and Review Board of Ontario. The Appeal and Review Board found that:

[T]he [anonymous] letters [by Dr. Koren] ... are shocking and outrageous, and constitute serious professional misconduct. ... They ... are inflammatory. They are of a bizarre nature. It would be reasonable for the Complainants to be fearful and intimidated. ... The letter-writing ... had the context of being planned and deliberate. Dr. Koren then maintained his denial [of authorship] throughout investigations until ... DNA [identified him] ... .

The Board finds that Dr. Koren’s conduct in relation to the letters is inexcusable ... and for reasons stated, the Board concludes that Dr. Koren has committed an act of professional misconduct, namely conduct unbecoming a physician.<sup>7</sup>

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\* On April 11, 2000, the University of Toronto and the Hospital for Sick Children imposed disciplinary action on Dr. Koren for “gross misconduct,” including persistent “lying,” in connection with the anonymous letters. The University and the Hospital said that his actions constituted “sufficient grounds for dismissal,” but they did not dismiss him, and imposed lesser penalties instead. (See Inquiry Report, section 5R(3) and 5R(4) for a discussion and citations.)

The Appeal Board Report found that the Complaints Committee had erred in considering that the discipline imposed on Dr. Koren by HSC and the University should be a significant factor in its decision. The Appeal Board Report said that:

The [Complaints] Committee, on behalf of the College [CPSO], has a responsibility to express a public concern. The anonymous letter-writing campaign merits condemnation by the College.<sup>8</sup>

The Appeal Board Report concluded, “the Board finds the failure of the [CPSO Complaints] Committee to place the matter into the disciplinary stream to be unreasonable,”<sup>9</sup> and directed the Complaints Committee to refer Dr. Koren’s conduct in the matter of the anonymous letters to the CPSO Discipline Committee. The Appeal Board also referred additional and separate allegations lodged by the Complainants against Dr. Koren back to the CPSO Complaints Committee for investigation:

The Board finds that the additional allegations relating to Dr. Koren’s medical research did form a part of the complaint of this complaint process, and were not adequately investigated. ... [T]he investigation has been inadequate and is returned to the [Complaints] Committee for further investigation.<sup>10</sup>

**D. Report by the Complaints Committee of the College of Physicians and Surgeons of Ontario (CPSO) on the allegations made by the Hospital for Sick Children (HSC) against Dr. Nancy Olivieri [Complaints Committee Report]**

The allegations that HSC and its MAC referred to the CPSO Complaints Committee were framed as “concerns,” namely:

- Dr. Olivieri continued to administer L1 to her patients after drafting a letter to the FDA on January 22, 1997 that presented the identification of an unexpected risk of L1 – progression of liver fibrosis.
- The liver biopsies for patients arranged by Dr. Olivieri in February and March 1997 may not have been clinically indicated and were performed for the purposes of research.
- Dr. Olivieri should have advised her Department Chief and co-workers about her concerns about liver toxicity.<sup>11</sup>

As discussed in the Inquiry Report (sections 5P and 5Q), these allegations had been brought to the MAC principally by Drs. Koren and O’Brodivich, and were believed by the MAC and HSC’s Board of Trustees. They were not disclosed to Dr. Olivieri and she therefore was deprived of a fair opportunity to respond. The allegations were publicly referred to CPSO (and very similar allegations also to the University) by HSC two weeks *after* HSC and the University had disciplined Dr. Koren for his dishonest actions in attempting to discredit Dr. Olivieri through anonymous letters.

The Complaints Committee of the CPSO reviewed the allegations in light of documents provided by the Hospital and a written submission by Dr. Olivieri. In addition:

The Committee was assisted in its review of this matter by an independent opinion provided by a panel of physicians holding senior academic positions, with expertise in paediatrics and thalassemia, liver pathology, clinical trials methodology, and bioethics. The panel thoroughly reviewed the College's investigative file . . . . In reaching its decision in this complaint, the Committee has relied on the analysis and conclusions arrived at by this highly qualified and experienced panel, which concluded that Dr. Olivieri did not fall below a reasonable standard of care in any of the areas of concern raised in this complaint.<sup>12</sup>

The Committee's decision was that "no action is warranted against Dr. Olivieri."<sup>13</sup>

As to the first allegation, the Complaints Committee concluded that risk of progression of liver fibrosis due to

continued use of L1 was not one of acute toxicity, and that there was therefore time to co-ordinate a safe and orderly transition to the standard treatment.<sup>14</sup>

The Complaints Committee Report said that Dr. Olivieri had "promptly" informed patients and their parents, and explained treatment options to them. The Complaints Committee Report also found that the situation facing Dr. Olivieri in early 1997 was one of balancing two chronic risks: the long known risk of liver and other organ damage due to iron loading in the absence of chelation treatment, and the newly identified risk that L1 itself could cause liver damage. The Report concluded that she had "ceased to administer L1 in a timely and expedient way, and in a manner which was in the best interests of her patients."<sup>15</sup>

The Complaints Committee Report concluded that the liver biopsies in question were clinically indicated and necessary to guide the future therapy of the patients concerned, so that the allegation of unnecessary use of this procedure was "not supported."<sup>16</sup> The Committee's Report added:

The Committee is of the opinion that Dr. Olivieri's judgment in advising patients to undergo biopsies was not only reasonable, but commendable in the circumstances.<sup>17</sup>

The CPSO Complaints Committee found no basis in practice or policy requiring Dr. Olivieri to provide "formal notification [to] her chief of staff."<sup>18</sup>

The Complaints Committee reported that its expert panel concluded "that Dr. Olivieri appeared very concerned about notifying all of the appropriate people," including "the clinical staff and her co-workers," and that she "was diligent in communicating and

publishing her data,” even though “the time frame for reporting the toxicity concerns was very compressed.”<sup>19</sup>

The CPSO Report said that on these points also:

The Committee agrees with the conclusion reached by the [expert] panel on this issue. The Committee is of the opinion that staged disclosure was appropriate in this case, and that Dr. Olivieri communicated diligently with those who required information regarding her concerns.<sup>20</sup>

In summary, the findings in the Inquiry Report (sections 5P and 5Q) on these matters have been independently confirmed both by the CPSO Complaints Committee and a panel of experts. It is of note that on December 28, 2001 a Toronto newspaper quoted a spokesperson for HSC as stating that, “the hospital does not plan to appeal the decision” of the CPSO Complaints Committee.<sup>21</sup>

### **E. The Dean’s Decision**

On January 7, 2002, Dean David Naylor wrote to Dr. Olivieri regarding the “very similar” allegations against her that HSC had referred to the University on the same day (April 27, 2000) HSC had referred allegations against her to CPSO.<sup>22</sup> The Dean’s letter said:

I decided to wait for the College’s [CPSO’s] assessment, and to dismiss the MAC [HSC] complaints if the College dismissed them. As a result [of the December 19, 2001 decision by the CPSO Complaints Committee], I have determined that the University will not be proceeding further with this matter, and the allegations are hereby dismissed.<sup>23</sup>

In his letter to Dr. Olivieri, Dean Naylor undertook to publish his action in the Faculty Council and in the *Canadian Medical Association Journal*. His decision to dismiss all allegations referred to the Faculty of Medicine was reported in the *University of Toronto Bulletin* on January 14, 2002.<sup>24</sup>

### **F. The December 2001 Commentary on the Inquiry Report by Drs. Naimark, Knoppers and Lowy [the Naimark Commentary]**

The Naimark Commentary endeavours to defend the 1998 Naimark Report against some of the criticisms of it in the Inquiry Report (section 5O). In this Supplement we discuss the following central points of difference between the Inquiry Report and the Commentary :

- The scope of the Naimark Report (the extent to which it fulfilled the mandate provided by the HSC Board of Trustees to the Naimark Review).
- The termination of the two Toronto L1 trials on May 24, 1996.



- Reporting obligations of Dr. Olivieri as the practitioner under Emergency Drug Release (EDR) at HSC during the period June 1996 – February 1997.
- The liver biopsies performed during the period February-March 1997 on some thalassemia patients who had been administered L1 under EDR.
- The time necessary to transfer patients from L1 treatment to standard therapy.

The Inquiry Report criticized the Naimark Report on a number of grounds, including that the Naimark Report did not address central issues such as: academic freedom; various aspects of the dispute between Dr. Olivieri and Apotex; Dr. Koren’s conflict of interest; the inconsistencies in Dr. Koren’s written testimony to the Naimark Review; and the role and responsibilities of the University of Toronto. The Naimark Commentary endeavours to defend the Naimark Report against these criticisms by saying that the Naimark Review’s scope was intentionally limited. In fact, the Board of Trustees gave the Naimark Review a broad mandate:

To conduct an independent review to determine the facts and circumstances giving rise to the current controversy involving Dr. Nancy Olivieri, The Hospital for Sick Children and Apotex Inc. including matters pertaining to the following:

- Patient Safety at the Hospital for Sick Children
- Conflicts of Interest
- Release and Publication of Research Information.<sup>25</sup>

The Naimark Commentary says in effect that the Naimark Review was not intended to address matters that were in fact encompassed by the mandate that it had. As discussed in the Inquiry Report, by not addressing central elements of the controversy, and by severing issues that were closely intertwined, the Naimark Review reached incorrect conclusions. For instance, as discussed below, by not addressing relevant facts and circumstances of the dispute between Dr. Olivieri and Apotex, the Naimark Report incorrectly concluded that the LA-01 and LA-03 trials had not been terminated by Apotex. This shortcoming of the Naimark Review was compounded by the fact that relevant documents were not available to it. For example, although at the outset of the Naimark Review in 1998 Apotex Vice-President Spino assured Dr. Naimark in writing that:

I have enlisted staff at Apotex to assemble *all* of the relevant correspondence pertaining to these issues into one place. ... you are welcome to spend as much time as you wish reviewing these documents ...<sup>26</sup> (emphasis added)

the Naimark Commentary says that the Naimark Review was “unaware of the 1995 contract pertaining to LA-03.”<sup>27</sup> It was in data from the LA-03 trial that Dr. Olivieri identified the two unexpected risks of L1. The 1995 contract for LA-03 expressly “supplanted” any other previous agreement on this trial, and expressly gave Apotex the right to terminate the LA-03 trial at any time (see Inquiry Report, section 5A). The

Naimark Report incorrectly concluded that the contract for the LA-01 trial also governed the LA-03 trial and on this basis reached other incorrect conclusions.

The Inquiry Report (section 5F) found that on May 24, 1996 Apotex simultaneously terminated both the randomized comparison trial (LA-01) and the long term trial (LA-03) of its drug L1 in Toronto. The Naimark Commentary (section 11), like the Naimark Report itself, holds that only Apotex’s sponsorship of these trials was terminated on that date, and that these trials continued for a further year.

The Inquiry Report (sections 5G(1), 5H(1), 5K and 5P) found that during the EDR treatment period, the patients were no longer under REB jurisdiction and Dr. Olivieri had no obligation to report adverse events to the REB. Whereas the Naimark Report itself held that she had such an obligation, the Naimark Commentary (pages 18 and 24-25) effectively acknowledges that its authors were unable to find conclusive evidence to support this claim, and thus that they were unable to contradict the Inquiry Report.

The Inquiry Report (sections 5K, 5P and 5Q) found that the biopsies in question were clinically indicated and necessary to guide the future therapy of the patients concerned, and that the transfer of patients from L1 treatment to standard therapy was effected in a timely and orderly manner. The CPSO Complaints Committee and its independent panel of experts reached the same conclusions (section D of this Supplement). Whereas the Naimark Report “did not take a position on the matter,”<sup>28</sup> its authors, in their Commentary (section 10), now appear to raise doubts about the appropriateness of these biopsies and the manner of transferring patients from L1 treatment to standard therapy.

While we do not consider it useful to discuss in detail all aspects of the Naimark Commentary, this should not be taken as acceptance of, or agreement with, statements, quotations or allegations in the Commentary regarding the Inquiry process, the Inquiry Report, individual members of the Committee of Inquiry, or the facts and circumstances of the case investigated. In the event we consider it necessary to respond further to the Commentary at a later date, we will do so. However, we do discuss below, in detail, three major areas of difference between the Inquiry Report and the Commentary.

## **1. The Trial Terminations**

The Inquiry Report (section 5H) found that Apotex had the right to terminate both Toronto trials of L1 and that, on May 24, 1996, it terminated both trials. In contrast, the Commentary states:

[T]he right to terminate does not mean that one necessarily has the power to terminate when the right is invoked.<sup>29</sup>

The Commentary states that the phrase “ ‘Apotex terminated the trials’ ” used in the Inquiry Report “could very well ... mean simply that Apotex discontinued sponsorship.”<sup>30</sup> Indeed the Commentary suggests that Apotex had incorrectly maintained

that it had done anything more than terminate its sponsorship:

It is, of course, clear why Apotex would have wished to maintain that the trials were terminated. They were not interested in having Dr. Olivieri continue to investigate a drug about which she had serious reservations.<sup>31</sup>

These statements in the Naimark Commentary are untenable in the face of the facts and circumstances of the case. Apotex had both the right *and* the power to terminate the trials, and exercised them with full and complete effect. A key event in the development of L1 during the 1990s was the acquisition by Apotex of the commercial rights to develop the drug for the treatment of iron overload. This was mentioned in the Naimark Report,<sup>32</sup> but neither that Report nor its authors' recent Commentary addressed the full consequences of this event, from which Apotex's right and power to terminate the trials derived. In view of these statements in the Naimark Commentary, it is necessary to review the relevant background.

The molecular structure of L1 was published scientifically in the early 1980s, so it could not be patented, as such. However, rights to develop L1 for medical use could be legally protected. Initially, the British Technology Group (BTG) held patent rights to develop L1 as a treatment for iron overload "in many countries including the US and Europe, but not in Canada."<sup>33</sup> Later, Ciba-Geigy, the manufacturer of the standard drug for iron overload (deferoxamine – DFO), acquired these rights from BTG and initiated development. Subsequently, however, Ciba-Geigy decided not to proceed and returned the rights to BTG. When, in 1988, Dr. Olivieri began preparations for her pilot study (which evolved into the long-term trial LA-03) with a group of patients who were non-compliant with the onerous DFO therapy, there was no commercial manufacturer of L1 in Canada.

Dr. R.A. McLelland in the Chemistry Department of the University of Toronto agreed to synthesize sufficient quantities for Dr. Olivieri's use in a trial. Drs. Olivieri and McClelland obtained the permission of "HPB [the Health Protection Branch of Health Canada] in September 1988,"<sup>34</sup> to synthesize the compound for medical use, initially "to provide the drug for open treatment of non-compliant patients through the Emergency Drug Release (EDR) Program," and later, "for the conduct of a physician sponsored trial."<sup>35</sup> This physician-sponsored clinical trial began when:

Following meetings with representatives of the Drugs Directorate, the investigators (Drs. Olivieri and Koren) filed their own IND [Investigational New Drug submission] in 1989.<sup>36</sup>

The protocol for this pilot study was approved by the HSC REB under the title, "Evaluation of Efficacy of the Oral Chelator L1 in Removal of Hepatic Iron in  $\beta$  Thalassemia Patients."<sup>37</sup> It was funded by research grants from the Medical Research Council of Canada (MRC) during the four-year period 1989-1993 (see Inquiry Report section 5A).

As discussed in the Inquiry Report (sections 5A and 5B), in 1993 Apotex acquired BTH's development rights for L1, in addition to development rights in Canada, and agreed to sponsor a new randomized comparison trial (LA-01) in Toronto, and a new short-term acute-toxicity trial (LA-02) at sites outside Canada, as well as the continuation of the pilot study in Toronto as a long-term trial (subsequently termed LA-03). From this time onward, the regulatory context of the Toronto L1 trials changed: there was a pharmaceutical manufacturer involved and supplying the drug. As such, Apotex assumed reporting obligations to Health Canada for these trials. This distinguished Apotex as a sponsor from any other sponsors (for instance, MRC was also a sponsor of the LA-01 trial, but MRC had no reporting obligations to Health Canada). Neither the Naimark Report nor the Commentary address the consequences of this crucial distinction among types of "sponsor." A 1994 internal company memo from by Apotex Vice-President Dr. Michael Spino summarized this important transition in the following terms:

[In the period prior to Apotex's involvement] Nancy ... obtained the chemical [L1] from Bob McClelland at U of T ... [and] ... obtained approval from HPB for a Phase II trial and conducted it herself without the support of industry. ... [Later,] Nancy and Gidi Koren approached Apotex to determine its interest in supporting the development of L1. We agreed to develop an appropriate formulation, conduct the necessary testing and support an MRC application. The project grew from one of support for the HSC team [by Apotex] to one of development of L1 by Apotex with the support of the clinical investigators.<sup>38</sup>

The application to MRC referred to by Dr. Spino was specifically for co-sponsorship of the new randomized trial LA-01. Pursuant to an agreement reached in March 1993, Apotex also began supplying L1 for the patients in the continuing pilot study (LA-03), under an Investigational New Drug Submission (INDS). An Apotex document summarizing the nature and purpose of the LA-03 trial stated:

Prior to October 1993 L1 was synthesized at the University of Toronto and encapsulated in gelatin capsules by the Pharmacy Department at the Hospital for Sick Children. After October 1993, compressed tablets of L1 (APO-66) manufactured as described in the INDS # 15828 (Rh Pharmaceuticals Inc. \*) were used in the treatment of these [LA-03] patients.<sup>39</sup>

The protocol for the ongoing long-term trial LA-03 was modified in recognition of Apotex's status as "the manufacturer" under the Food and Drugs Act and Regulations, and as the legal owner of the development rights to L1. This trial was henceforth no longer simply Dr. Olivieri's trial. HSC's REB approved substantial modifications of the 1991 protocol for the pilot study (LA-03), one dated October 1993 and the other September 1995. Specific obligations for Drs. Olivieri and Koren as "investigators," and for Apotex as "sponsor," were written into the LA-03 protocol. For instance, for the investigators, the September 1995 protocol specified:

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\* The Apotex subsidiary through which Apotex's development of L1 was initially conducted. Rh Pharmaceuticals Inc. is located on the campus of the University of Manitoba (see Inquiry Report, section 5N, endnote 5).

The investigators in this trial will conduct the study as described in the Health Protection Branch Drugs Directorate Guidelines entitled “Conduct of Clinical Investigations” (see Appendix 1).<sup>40</sup>

Appendix 1 consisted of a complete copy of the HPB guidelines “Conduct of Clinical Investigations” published by Health and Welfare Canada in 1989. For the purposes of this discussion, it is relevant to note a provision of these guidelines:

#### 7 ADHERENCE TO THE PROTOCOL

The responsible clinical investigator must adhere to the protocol agreed upon in advance by the sponsor, the responsible clinical investigator, the Independent Review Committee, and the Health Protection Branch. While latitude is sometimes necessary, significant changes in the study design, agreed between the sponsor and the responsible clinical investigator, must be submitted to the Independent Review Committee and the Health Protection Branch.<sup>41</sup>

The September 1995 LA-03 protocol specified obligations for Apotex as the sponsor consistent with those for the manufacturer specified in section C.08.005 (1) and (2) of the Food and Drugs Act and Regulations pertaining to clinical trials (as distinct from section C.08.010 pertaining to Emergency Drug Release – see below). The term sponsor in this context has a precise definition that is set out in the HPB guidelines “Conduct of Clinical Investigations” appended to the LA-03 protocol, namely:

The sponsor is *defined* as the manufacturer of the drug, as stated in the Food and Drugs Act and Regulations.<sup>42</sup> (emphasis added)

This definition is important because a contributing factor to the erroneous conclusions of HSC REB Chair Dr. Aideen Moore, the Naimark Report and the Naimark Commentary is their confusion over sponsorship. In common discourse, a trial sponsor is an agency providing funding support, such as the Medical Research Council (MRC), a private foundation or a pharmaceutical manufacturing corporation. However, sponsors like MRC (now CIHR) or a foundation do not have reporting obligations under the Food and Drugs Act and Regulations, whereas the pharmaceutical manufacturer of a specific drug has such legal reporting obligations respecting a clinical trial of its drug.

In particular, this LA-03 protocol specified the following:

#### SPONSOR OBLIGATIONS [LA-03]:

- provide adequate support to the principal investigator so that the trial may be conducted safely and effectively;
- must consider the recommendations of the Data and Safety Monitoring Board;
- provide study medication and relevant study materials (case report forms);
- monitor the study;
- report the occurrence of all adverse events to regulatory agencies;

- report the findings of this study annually, or more frequently, to regulatory agencies and to provide a written report of the study on its [sic] completion;
- retain all documentation and records as required by the relevant regulatory agencies.

In concrete recognition of Apotex's power in the situation, the executed contracts between Apotex and Dr. Olivieri and her co-investigator Dr. Koren – one for each of the LA-01 and LA-03 trials – expressly stated that Apotex had the right to terminate these trials, unilaterally, at any time. In conformity with these contract provisions, the revised patient information and consent forms Dr. Olivieri submitted to the REB for approval on May 20, 1996 expressly stated that the trials could be terminated unilaterally at any time by Apotex.

These new information and consent forms also explained the unexpected risk of L1 – loss of sustained efficacy – recently identified by Dr. Olivieri. As discussed in the Inquiry Report (section 5F), it was submission of these revised forms to the REB explaining this risk to patients, an action taken by Dr. Olivieri on direction of the REB, that precipitated the trial terminations. A few days later, on Friday, May 24, 1996, Apotex wrote to the investigators, Dr. Olivieri and Dr. Koren, notifying them that:

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. The Research Ethics Boards of each of these institutions and the Health Protection Branch will be informed of this action by the Sponsor.

Steps to be undertaken to close-out the LA-01 *and* LA-03 studies are as follows:

- *All study medication remaining at the sites must be immediately returned to the Sponsor as per Drugs Directorate Guideline, Conduct of Clinical Investigations, section 9. ...*
- *“Close-out” assessments must be performed for all patients as per the protocol.*
- *All study related materials such as Case Report Forms, Protocols and Investigator’s Brochures must be returned to the sponsor at the time of the “Close-out visit.”<sup>43</sup> (emphasis added)*

On the same day, in a recorded telephone message to Dr. Olivieri, Apotex Vice-President Dr. Michael Spino repeated this notification. Drs. Naimark, Knoppers and Lowy suggest that these notifications of trial terminations could have been mere figures of speech. However, the company immediately notified Health Canada that it had terminated both trials, and it retrieved all supplies of its drug L1 from the hospital's pharmacy (see Inquiry Report, section 5F, for citations).

Therefore, in May 1996, Apotex fully and effectively exercised not only its right, but its power, and terminated both trials, LA-01 and LA-03.

Drs. Olivieri and Koren immediately communicated this event in writing to the physicians-in-chief of both hospitals, the REB Chair, the University's Dean of Medicine Dr. Arnold Aberman, and others. In their letter dated May 25, 1996, they wrote, "we received a letter terminating both studies,"<sup>44</sup> and they outlined their concerns arising from Apotex's precipitous terminations, as well as its accompanying warnings of legal action should they disclose information about the risks to patients or others. In early June 1996, Dean Aberman attempted to mediate between Apotex and the investigators who felt that the trials should be allowed to continue for those fully informed patients who appeared to be benefiting. The Dean reported that "Apotex would not change their position on discontinuing the clinical trials."<sup>45</sup> Dean Aberman reported that, instead, "Apotex agreed to the Emergency Release of L1 to any patient who was on L1 during the trial."<sup>46</sup> Thus Apotex agreed to continuation of treatment of patients in an Emergency Drug Release (EDR) arrangement.

It is documented that the proposed new arrangement, under EDR, was accepted by Health Canada and was implemented (Inquiry Report, section 5G), after Health Canada had received Apotex's notification that it had terminated both trials. This type of release of an unproven drug is covered in a different section of the Food and Drugs Act and Regulations (section C.08.010) than that for clinical trials (section C.08.005). Under the EDR provisions, it was now Dr. Olivieri as the practitioner, not Apotex as the manufacturer, who was legally obligated to report the results of treatment, including adverse drug reactions, directly to Health Canada.

The REB of HSC had been informed of the May 24, 1996 trial terminations by copy of the May 25, 1996 letter sent by Drs. Olivieri and Koren. Later, in July 1996, Dr. Olivieri and her division chief in Hematology at HSC, Dr. M. Freedman, sent the REB formal written notifications of the terminations. Both notifications were on official REB reporting forms, and both were stamped as received by the REB on August 1, 1996. The one pertaining to the long-term (LA-03) trial specified as "Project Title" the original title as approved by the REB in 1990, "Evaluation of Efficacy of the Oral Iron Chelator L1 in Removal of Hepatic Iron in  $\beta$  Thalassemia Patients," and notified the REB that:

Study terminated prematurely\* by Apotex Pharmaceuticals on May 24, 1996.<sup>47</sup>

The similar notification for LA-01 said:

Apotex Pharmaceuticals prematurely<sup>+</sup> terminated this study on May 24, 1996.<sup>48</sup>

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\* The October 1995 contract for the LA-03 trial had provided for substantial funding by Apotex for the next two years.

<sup>+</sup> The three-year April 1993 contract for LA-01 had expired, but negotiations between Apotex and Dr. Olivieri for a renewal were underway in the weeks immediately preceding the May 24, 1996 terminations. Here "prematurely" means that a substantial number of trial subjects had not completed the specified two-year study period.

In summary, both trials had been terminated by Apotex in May 1996, the company formally notified Health Canada, and Dr. Olivieri and her immediate clinical supervisor Dr. Freedman formally notified the REB.

As noted in the Inquiry Report (section 5O), the Naimark Report held that neither of the LA-01 and LA-03 trials had been terminated in May 1996, that instead only Apotex's sponsorship had been terminated and the two "L1 trials" themselves continued until they "were stopped at the end of May 1997."<sup>49</sup> The Commentary appears less sweeping on this point. It presents (at pages 20 and 21) testimony from records maintained by Dr. Aideen Moore (who became REB Chair in July 1996, following the trial terminations) and her assistant that the LA-03 trial continued into 1997, but presents nothing comparable on LA-01.

In fact, Dr. Moore was mistaken, as discussed in the Inquiry Report (sections 5H, 5K and 5P). She made several significant errors of fact and interpretation and these were reflected in REB records. She appears to have confused continuation of treatment under EDR with continuation of one of the terminated trials. For instance, Dr. Moore wrote that the randomized trial LA-01 trial "was terminated on May 24, 1996," but that the LA-03 trial "continued."<sup>50</sup> However, as noted above, Apotex had the equivalent right and power to terminate the LA-03 trial, and did terminate the LA-03 trial as well, on the same day, May 24, 1996, that it terminated the LA-01 trial. Indeed it was in data from this long-term trial LA-03 that the unexpected risk of loss of sustained efficacy was identified – and it was in an effort to prevent disclosure of this unexpected risk that Apotex terminated both trials.

The Naimark Commentary cites a letter by Dr. Moore's assistant saying that the "[LA-03] project was approved for the period of one year by the Research Ethics Board in June, 1996."<sup>51</sup> However, any such purported approval was nullified by the action of Apotex, formally communicated to the REB by Drs. Olivieri and Freedman in July 1996, as noted above. The REB did not have the administrative or legal authority to reinstate a trial that had been terminated by the manufacturer.

The Naimark Commentary (page 22) relies on a truncated definition of "protocol" to bolster its argument that the LA-03 trial, somehow, continued after it was terminated by the action of the manufacturer, Apotex. However, as noted above, the LA-03 protocol stated that the LA-03 trial was to be conducted in accordance with Health Canada's Drug Directorate Guidelines on Conduct of Clinical Investigations published in 1989 and included as Appendix A to this protocol. The definition of "PROTOCOL" in these Guidelines includes, "the conditions under which it [the trial] it is to be performed and managed."<sup>52</sup> As quoted above, the LA-03 protocol contained explicit performance and management provisions that were to be implemented by Apotex. After May 24, 1996, these conditions could not be met, and at Dean Aberman's mediation meeting of June 7, 1996 this was confirmed. Furthermore, the title page of the LA-03 trial protocol stated:



The information contained in this protocol is the *property* of Apotex Research Inc.<sup>53</sup> (emphasis added)

It appears that, like Dr. Moore and her assistant, either Drs. Naimark, Knoppers and Lowy did not carefully read, or misinterpreted relevant documents, such as the LA-03 protocol or the relevant sections of the Food and Drugs Act and Regulations, since their Commentary says:

In the case of a clinical investigation the protocol is active as long as the plan is being followed.<sup>54</sup>

As a result of Apotex's action in exercising its rights and powers, the plan could not be followed, so the protocol had been de-activated (terminated).

## **2. Reporting obligations in EDR treatment arrangements**

Some patients who had been enrolled in one or the other of the two terminated trials did not wish to return to the onerous DFO therapy. Apotex refused to reinstate either trial, but Dean Aberman mediated an agreement between Apotex and Dr. Olivieri in which the company agreed to supply L1 under Health Canada's EDR program for use in a treatment arrangement in the period following the termination of the LA-01 and LA-03 trials. For her part, Dr. Olivieri agreed to continue to administer the drug, under EDR, to those patients who wished to continue on it and who were still seen to be benefiting from it, provided the known risks were disclosed to them and they or their families agreed to accept the risks.

In agreeing to the EDR release of L1 which, in the terminology of the Food and Drugs Act and Regulations was "a new drug," that is, a drug whose safety and effectiveness had not been established, Apotex, the manufacturer, thereby agreed to the EDR regulatory requirement on Dr. Olivieri. Namely, as the practitioner, she must report the results of treatment, including any adverse drug reactions, to Health Canada and to the manufacturer. For an iron chelation drug, any lack of efficacy that might be identified in the monitoring would be an adverse drug reaction, as would any toxicity. To meet this legal requirement, Dr. Olivieri had to monitor the patients. Since they would be on an unproven drug, the monitoring regime would be more intensive than if they were on standard therapy. Thus on this account, the patients were informed that the drug they were continuing on was an unproven drug and that the monitoring would be necessary.

The post-trial provision of L1 under EDR was agreed to between Apotex and Dr. Olivieri, approved by Health Canada, and implemented without the involvement of the HSC REB.<sup>55</sup> At HSC at that time, among the several types of "studies [i.e., research]" that "d[id] not need approval of HSRC [REB]," was the monitoring of patients being administered an experimental drug under EDR.<sup>56</sup> This fact was published by Dr. Koren in a book chapter on the oversight of clinical research at HSC, in 1993. At that time he was Associate Director for Clinical Research in HSC's Research Institute and had just completed a substantial term as Chair of HSC's REB.

The Commentary appears unwilling to accept this:

As of this writing we are unable to confirm the statement in the CAUT Report [the Inquiry Report] that "... under HSC policy, Dr. Olivieri was not required to obtain REB approval to treat patients under EDR." ... We are continuing to look into the matter.<sup>57</sup>

It is reasonable to infer that Drs. Naimark, Knoppers and Lowy were also unable to deny this conclusion in the Inquiry Report (discussed in sections 5G(1), 5H(1), 5K(7), 5P(9) and 5P(10)). As noted in the Inquiry Report, Dr. O’Brodivich, Dr. Koren and others at HSC put forward several alleged bases for faulting Dr. Olivieri’s conduct, yet none of them, nor the authors of the Commentary, have put forward evidence that Dr. Olivieri was required to obtain REB approval to treat patients under EDR. If there had been any such policy in force, there can be no doubt it would have been brought forward sometime in the five years that have elapsed since February 1997, when Dr. O’Brodivich first (incorrectly) suggested there was such an obligation.

As found in the Inquiry Report, under EDR, Dr. Olivieri was legally obligated to report adverse drug reactions to Health Canada and to Apotex, and ethically obligated to inform her patients. She met these obligations and she had *no other* reporting obligations. Independently, the Report of the CPSO Complaints Committee found that in the EDR treatment arrangement of 1996-1997, "Dr. Olivieri communicated diligently with those who required information regarding her concerns [regarding the risk of progression of liver fibrosis]."<sup>58</sup> Furthermore, on January 7, 2002, Dean Naylor "dismissed" the "very similar" allegations that HSC and its MAC had referred to the University’s Faculty of Medicine.<sup>59</sup> Among the allegations referred to the Faculty of Medicine was the specific allegation that:

Dr. Olivieri should have reported her conclusions with respect to L1 toxicity to the Research Ethics Board [REB].<sup>60</sup>

This was the adverse finding against Dr. Olivieri in the December 1998 Naimark Report. In April 2000 this was expressly referred to the Faculty of Medicine by HSC and its MAC. It was still maintained in the December 2001 Commentary. It has now been *dismissed* by the Dean of the Faculty of Medicine.

### **3. The care of patients and the liver biopsies performed on some of them in February-March 1997**

The Commentary suggests that, had Dr. Olivieri reported the second risk she identified to the REB, the subsequent treatment of some patients who had been on L1 might have been different. However, the documentary record available to the authors of the Commentary shows that after Dr. Olivieri did report to the REB, on the insistence of Dr. O’Brodivich, the REB did not propose any course of action different from that of Dr. Olivieri. Indeed, neither the Chair, Dr. Moore, nor any other member had the relevant expertise to question

Dr. Olivieri's judgment about clinical management of these patients. Nor did the REB feel it necessary to seek independent expert advice – Dr. Olivieri's clinical assessment as an internationally recognized expert was accepted by the REB. Thus, in fact, reporting to the REB made no material difference to the management of patient care.

For reasons that are not explained, the Naimark Commentary goes beyond the Naimark Report and raises explicit questions about the propriety of the liver biopsies performed on some patients after the second risk had been identified, and about administration of the drug L1 in this period. The questions reveal a misunderstanding of the facts and circumstances. The Commentary says:

[T]he issue is ... whether the patients who “remained on the study” were exposed to increased frequency of liver biopsies compared to those who did not and whether that exposure continued to be acceptable even though a conclusion had been reached that the drug should not be administered on grounds of toxicity.<sup>61</sup>

Regarding these topics, the Commentary also says:

The CAUT Report [Inquiry Report] correctly points out that the [Naimark] Review did not take a position on the matter. The reason the [Naimark] Review Panel did not do so is that the Review was not intended to adjudicate disputes about specific clinical practices.<sup>62</sup>

In fact, at the time (1997) of these events, there was no medical basis for a “dispute” about these clinical practices and hence no need for “adjudication.” The necessity of liver biopsy to guide the therapy of transfusion-dependent thalassemia patients was established in the medical literature. Also, given the possibility of chronic liver toxicity of L1 (progression of hepatic fibrosis) in these patients, it was necessary to assess whether this had occurred, by liver biopsy. The chronic risk of harm to the liver, heart and other organs from iron loading in transfusion-dependent patients in the absence of iron-chelation therapy was also well documented.<sup>63</sup> Thus both the need for biopsy, and the appropriateness of an orderly transition back to standard therapy were well documented – both of which Dr. Olivieri did. The authors of the Naimark Report and the Naimark Commentary had the same opportunity to review the relevant literature as did the authors of the Inquiry Report. Indeed, because it was clear from the literature that there was no medical basis for a genuine dispute about the appropriateness of her conduct, the Committee of Inquiry reviewed the documentary record to trace the origins of these questions which are, in essence, allegations against Dr. Olivieri.

In the documentary record available both to the Naimark Review and the Committee of Inquiry, these medical questions or “issues” appear first to have been raised by Apotex (see Inquiry Report, section 5Q), specifically the company's Vice-President Dr. Spino who is a pharmacologist. The company had an interest in discrediting the use of liver biopsy, because the two unexpected risks of its drug identified by Dr. Olivieri (loss of sustained efficacy and progression of liver fibrosis) were identified through biopsy data (hepatic iron concentrations and hepatic histology). In a letter to Dr. Naimark dated

November 24, 1998, Apotex Vice-President Dr. Spino outlined these “issues” in terms very similar to those in which they are now put forward in the Naimark Commentary (as quoted above):

We [Apotex] could not understand how Dr. Olivieri could have continued to give a drug, if she believed it to be toxic to patients, in order to collect more hepatic biopsy data.<sup>64</sup>

In fact, the biopsies in question were not done in accordance with any planned monitoring frequency under EDR. They were done because they were necessary to guide future therapy and were clinically indicated. A risk of chronic toxicity had been identified through review of historical data of one group of patients who had been on L1 (those who had been in the long-term trial LA-03). This was the clinical indication to assess the patients who had been in the other trial (LA-01), namely, to determine whether any of them had experienced this adverse effect from L1 treatment. The biopsy results were also necessary in order to determine the future course of therapy for each individual (how soon DFO administration should be commenced and at what dosage level). The Inquiry Report and independently, the CPSO Complaints Committee Report, explain the relevant facts on these two “issues.” As stated in the Complaints Committee Report, first:

The [Complaints] Committee is of the opinion that Dr. Olivieri’s judgment in advising patients to undergo biopsies was not only reasonable, but commendable in the circumstances.<sup>65</sup>

and second:

The panel [of experts convened by CPSO] concluded that Dr. Olivieri ceased to administer L1 in a timely and expedient way, and in a manner which was in the best interests of her patients. ... [T]he risk that the patients were facing ... was not one of acute toxicity ... . [T]he [CPSO Complaints] Committee is of the opinion that Dr. Olivieri acted reasonably and appropriately in the manner in which she terminated the use of L1 in her patients after learning of the potential toxicity of the drug.<sup>66</sup>

## **G. Exoneration of Dr. Olivieri**

Dr. Olivieri has now been exonerated by the Committee of Inquiry, by the independent panel of experts convened by the CPSO Complaints Committee and the Complaints Committee itself, and by the Dean of the Faculty of Medicine of the University of Toronto. However, the publicity received by the Naimark Report, by the HSC Board’s referral of Dr. Olivieri to HSC’s disciplinary body (the MAC), and by HSC’s referral of Dr. Olivieri to the CPSO Complaints Committee and to the University, has resulted in widespread misunderstandings. Because of this, we summarize here the main points.

- The two Toronto trials of L1 were terminated on May 24, 1996. Thereafter, some patients who did not wish to return to the onerous standard therapy were continued on L1, provided they were still benefiting from it, were informed of and accepted the known risks of L1, and agreed to necessary monitoring of the effects of treatment with this unproven drug. During this treatment period, Apotex was authorized by Health Canada to supply L1 under Emergency Drug Release (EDR).
- There was no policy requiring Dr. Olivieri to seek REB approval for treatment of patients under EDR, and no policy requiring her to inform the REB of the effects of treatment, including any adverse effects identified during EDR treatment.
- During the EDR treatment period in 1996 and 1997, Dr. Olivier's actual reporting obligations were: the legal requirement to report the effects of treatment, including any adverse effects, to Health Canada and to the manufacturer, Apotex; and the ethical requirement to inform patients of any adverse effects.
- In early February 1997, Dr. Olivieri identified a new unexpected adverse effect, progression of liver fibrosis. She then fulfilled all three of her reporting obligations (to patients, to Health Canada and to Apotex) in a timely manner.
- In February 1997, Dr. Olivieri counselled those patients who had been on L1 and who had not recently had a liver biopsy to undergo one. These liver biopsies were clinically indicated. They were not, in the circumstances, a research procedure. Because the patients being treated under EDR were not under REB jurisdiction, and because the biopsy procedure itself was clinically indicated, there was no requirement to seek REB approval for it. Dr. Olivieri's judgment in regard to these biopsies was found by the CPSO Complaints Committee to have been "not only reasonable, but commendable in the circumstances," as cited earlier.
- Dr. Olivieri effected the transfer of patients from L1 to standard therapy "in a timely and expedient way, and in a manner which was in the best interests of her patients," as the CPSO Complaints Committee also found (cited earlier).
- Dr. Olivieri subsequently published findings on L1 on the basis of data from patients' charts, including data from the biopsies performed on some patients in early 1997. There was no policy requiring her to seek REB permission to publish findings based on review of patients' charts. It is important to note that when the Canadian "Tri-Council Policy Statement: Ethical Conduct of Research Involving Humans" came into force in the following year (1998), new reporting requirements were imposed on researchers in all universities and affiliated hospitals which receive funding from the federal granting councils. For, instance, chart review research henceforth required REB approval. However, such requirements cannot be imposed retroactively, and so it is clear that the REB did not have jurisdiction over the chart review, and clear that Dr. Olivieri did not fail in any obligation with respect to the REB in this matter.

- When Dr. Olivieri did inform the REB of the new risk and of her clinical actions, because Dr. O’Brodivich insisted she do so and not because any policy required this, there was *no material difference* in the subsequent care of patients.

## **H. Findings and Conclusions**

1. The Appeal Board Report confirmed the gravity of the misconduct by Dr. Koren in the matter of the anonymous letters, and noted that such misconduct by a physician is a matter of public interest requiring referral to the CPSO Discipline Committee. The Appeal Board Report directed the CPSO Complaints Committee to refer Dr. Koren to the CPSO Discipline Committee in the matter of the anonymous letters, and to investigate complaints of other alleged misconduct by Dr. Koren that had been lodged with the Complaints Committee but which it had not investigated.
2. The December 2001 Report of the CPSO Complaints Committee concluded that all “questions” regarding Dr. Olivieri’s conduct referred to CPSO by HSC and its MAC were unfounded. It independently confirms the findings of the October 2001 Inquiry Report on all matters they both considered.
3. In January 2002, Dean Naylor dismissed all allegations referred to the University’s Faculty of Medicine by HSC and its MAC. The Dean’s decision was contingent on and followed the CPSO Complaints Committee Report. The allegations he dismissed included the allegation that, “Dr. Olivieri should have reported her conclusions with respect to L1 toxicity to the Research Ethics Board.” This allegation, now dismissed, was the adverse conclusion against Dr. Olivieri in the December 1998 Naimark Report, that was repeated in the December 2001 Naimark Commentary.
4. The Naimark Commentary on the Inquiry Report contains incorrect conclusions on central matters of the L1 controversy, including those pertaining to the conduct of Dr. Olivieri.

The Naimark Commentary goes beyond the original Naimark Report in discussing topics that were central to allegations Apotex made against Dr. Olivieri in 1998, central to allegations Drs. Koren and O’Brodivich made to the MAC in 1999, and central to allegations HSC and its MAC referred to CPSO in 2000. These concern management of the care of patients who had continued on the iron chelation drug deferiprone (L1) under EDR after the drug manufacturer Apotex had terminated the Toronto L1 trials in May 1996. Specifically, these allegations were: that liver biopsies performed on some of these patients in February and March 1997 were not necessary and were done for research purposes; and that the transfer of patients from L1 treatment to standard therapy was not effected in a timely manner. The discussion of these matters in the Naimark Commentary indicates that its authors have seriously misunderstood important matters – matters that were in fact clearly explained in HSC documents available to the Naimark Review and in the relevant medical literature. These biopsies were clinically indicated and patients were transferred to standard therapy in a timely way.

The Naimark Commentary contains no evidence that contradicts any material aspect of the Inquiry Report.

5. Dr. Olivieri has been exonerated by the Committee of Inquiry (October 26, 2001), by the independent panel of experts convened by the CPSO Complaints Committee and the Complaints Committee itself (December 19, 2001), and by the Dean of the Faculty of Medicine of the University of Toronto (January 7, 2002).

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<sup>1</sup> J. Thompson, P. Baird and J. Downie, *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.*, co-published by the Canadian Association of University Teachers and James Lorimer & Company, Toronto, 2001, and available in electronic form at [www.dal.ca/committeeofinquiry](http://www.dal.ca/committeeofinquiry)

<sup>2</sup> Health Professions Appeal and Review Board of Ontario, “Decision and Reasons” dated October 11, 2001 “Regarding a Request to Review a Decision of the Complaints Committee of the College of Physicians and Surgeons of Ontario,” “Concerning a Complaint Filed with the College” by Drs. Helen Chan, Peter Durie and Brenda Gallie, “Regarding the Member [of CPSO] Gideon Koren, MD.”

See also the news article on this Report of the Appeal and Review Board in the *National Post*, November 22, 2001.

<sup>3</sup> CPSO “Complaints Committee Decision and Reasons” issued December 19, 2001, available on the CAUT website, [www.caut.ca](http://www.caut.ca)

<sup>4</sup> Letter, D. Naylor to N. Olivieri, issued January 7, 2001 by e-mail at 11:55 PM

<sup>5</sup> A. Naimark, B.M. Knoppers and F.H. Lowy, “Commentary on selected aspects of the Report of the CAUT Committee of Inquiry on the Case Involving Dr. Nancy Olivieri, the Hospital for Sick Children, the University of Toronto, and Apotex Inc.,” December 2001, HSC website, [www.sickkids.on.ca/mediaroom/CAUTfinal2ed.pdf](http://www.sickkids.on.ca/mediaroom/CAUTfinal2ed.pdf)

<sup>6</sup> Appeal Board Report, pages 4, 5

<sup>7</sup> Appeal Board Report, page 11

<sup>8</sup> Appeal Board Report, pages 11, 12

<sup>9</sup> Appeal Board Report, page 11

<sup>10</sup> Appeal Board Report, page 12

<sup>11</sup> Letter, L. Becker (Chair of HSC MAC) to Complaints Committee, CPSO, May 2, 2000

<sup>12</sup> CPSO “Complaints Committee Decision and Reasons” issued December 19, 2001, page 16

<sup>13</sup> CPSO “Complaints Committee Decision and Reasons” issued December 19, 2001, page 16

<sup>14</sup> CPSO “Complaints Committee Decision and Reasons” issued December 19, 2001, page 16

<sup>15</sup> CPSO “Complaints Committee Decision and Reasons” issued December 19, 2001, page 16

<sup>16</sup> CPSO “Complaints Committee Decision and Reasons” issued December 19, 2001, page 17

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- <sup>17</sup> CPSO “Complaints Committee Decision and Reasons” issued December 19, 2001, page 17
- <sup>18</sup> CPSO “Complaints Committee Decision and Reasons” issued December 19, 2001, page 17
- <sup>19</sup> CPSO “Complaints Committee Decision and Reasons” issued December 19, 2001, page 17
- <sup>20</sup> CPSO “Complaints Committee Decision and Reasons” issued December 19, 2001, page 17
- <sup>21</sup> News article, Toronto Star, December 28, 2001
- <sup>22</sup> Letter, D. Naylor to N. Olivieri, January 7, 2002
- <sup>23</sup> Letter, D. Naylor to N. Olivieri, January 7, 2002
- <sup>24</sup> Article in University of Toronto *Bulletin*, January 14, 2002, page 3
- <sup>25</sup> Naimark Report, December 1998, page 1 – the quotation is from the HSC Board resolution of September 8, 1998, setting out “the mandate” of the Naimark Review
- <sup>26</sup> Letter, M. Spino to A. Naimark, September 24, 1998
- <sup>27</sup> A. Naimark, B.M. Knoppers and F.H. Lowy, “Commentary” on the Inquiry Report, December 2001, page 23, HSC website
- <sup>28</sup> A. Naimark, B.M. Knoppers and F.H. Lowy, “Commentary” on the Inquiry Report, December 2001, page 16, HSC website
- <sup>29</sup> A. Naimark, B.M. Knoppers and F.H. Lowy, “Commentary” on the Inquiry Report, December 2001, page 23, HSC website
- <sup>30</sup> A. Naimark, B.M. Knoppers and F.H. Lowy, “Commentary” on the Inquiry Report, December 2001, page 21, HSC website
- <sup>31</sup> A. Naimark, B.M. Knoppers and F.H. Lowy, “Commentary” on the Inquiry Report, December 2001, page 22, HSC website,
- <sup>32</sup> Naimark Report, published by HSC December 9, 1998, page 20
- <sup>33</sup> memo, M. Spino (Apotex) to M. Woloski and other Apotex staff, June 25, 1994
- <sup>34</sup> Letter, R.A. McClelland to the Scientific Review Committee, Medical Research Council of Canada, September 10, 1988
- <sup>35</sup> Inquiry Report, page 448
- <sup>36</sup> Apotex Research Inc., “Clinical Summary – LA-03” submitted to Health Canada, January 26, 1998, page 2.
- Dr. Olivieri’s preclinical New Drug Submission to the Health Protection Branch (HPB) of Health and Welfare Canada for the pilot study of L1 (that after 1993 became the LA-03 trial) had “control number 8HP882162.” (See, for instance, the letter, D. Cook (HPB) to N. Olivieri, March 26, 1991.)
- <sup>37</sup> Inquiry Report, page 103-104, citing REB approved protocol from 1990
- <sup>38</sup> Memo, M. Spino to M. Woloski et al., June 25, 1994



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- <sup>39</sup> A two-page (undated) Rh Pharmaceuticals Inc. summary of the nature and purpose of the LA-03 trial, appended to the September 27, 1995 LA-03 protocol
- <sup>40</sup> LA-03 trial protocol, “Protocol Modification # 2,” dated September 27, 1995, original version dated March 1991, with ” Protocol Modification # 1” dated October 1993, page 5
- <sup>41</sup> “Drug Directorate Guidelines” on “Conduct of Clinical Investigations,” Health and Welfare Canada, 1989, page 11
- <sup>42</sup> “Drug Directorate Guidelines” on “Conduct of Clinical Investigations,” Health and Welfare Canada, 1989, page 1
- <sup>43</sup> Letter, M. Spino to N. Olivieri and G. Koren, May 24, 1996
- <sup>44</sup> Letter, N. Olivieri and G. Koren to R. Haslam, with copies to other hospital and university administrators, May 25, 1996
- <sup>45</sup> E-mail, A. Aberman to P. Durie et al., August 30, 1998, summarizing results of A. Aberman’s mediation meeting on June 7, 1996 involving the investigators and Apotex
- <sup>46</sup> E-mail, A. Aberman to P. Durie et al., August 30, 1998, summarizing results of A. Aberman’s mediation meeting on June 7, 1996 involving the investigators and Apotex
- <sup>47</sup> Trial termination report to REB signed by N. Olivieri and M. Freedman – signed by Olivieri on July 20, 1996 and by Freedman on July 25, 1996, stamped as received by the REB on August 1, 1996
- <sup>48</sup> Trial termination report to REB signed by N. Olivieri and M. Freedman – signed by Olivieri on July 21, 1996 and by Freedman on July 25, 1996, stamped as received by the REB on August 1, 1996
- <sup>49</sup> Naimark Report, published by HSC December 9, 1998, pages 30, 35 and 135 (the quotation is from page 135)
- <sup>50</sup> Letter, A. Moore to H. O’Brodivich, February 27, 1997 (see Inquiry Report, section 5K(7) for discussion)
- <sup>51</sup> A. Naimark, B.M. Knoppers and F.H. Lowy, “Commentary” on the Inquiry Report, December 2001, page 21, HSC website
- <sup>52</sup> “Drug Directorate Guidelines” on “Conduct of Clinical Investigations,” Health and Welfare Canada, 1989, page 19
- <sup>53</sup> LA-03 trial protocol, dated September 27, 1995
- <sup>54</sup> A. Naimark, B.M. Knoppers and F.H. Lowy, “Commentary” on the Inquiry Report, December 2001, page 21, HSC website
- <sup>55</sup> See Inquiry Report, sections 5G(1) and 5H(1), and the letter cited therein from M. Woolcock (Apotex) to N. Olivieri, dated June 27, 1996 confirming that Health Canada had authorized Apotex to provide L1 under EDR, and noting Dr. Olivieri’s reporting obligations to Health Canada and Apotex on the results of treatment.
- <sup>56</sup> Inquiry Report, section 5P(9)), quoting from a chapter written by Dr. Gideon Koren in the “Textbook on Ethics in Pediatric Research” he edited, published by Krieger Publishing Co., Malabar, Florida 1993).

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<sup>57</sup> A. Naimark, B.M. Knoppers and F.H. Lowy, “Commentary” on the Inquiry Report, December 2001, pages 24, 25, HSC website

<sup>58</sup> CPSO “Complaints Committee Decision and Reasons” issued December 19, 2001, page 18

<sup>59</sup> Letter, D. Naylor to N. Olivieri, January 7, 2002

<sup>60</sup> Letter, L. Becker (Chair, HSC MAC) to E. Phillipson (Chair, Department of Medicine – N. Olivieri’s department in the UT Faculty of Medicine), May 2, 2000

<sup>61</sup> A. Naimark, B.M. Knoppers and F.H. Lowy, “Commentary” on the Inquiry Report, December 2001, pages 16, 17, HSC website

<sup>62</sup> A. Naimark, B.M. Knoppers and F.H. Lowy, “Commentary” on the Inquiry Report, December 2001, pages 16, HSC website

<sup>63</sup> See Inquiry Report, sections 5K and 5Q

<sup>64</sup> Letter, M. Spino to A. Naimark, November 24, 1998, page 3

<sup>65</sup> CPSO “Complaints Committee Decision and Reasons” issued December 19, 2001, page 17

<sup>66</sup> CPSO “Complaints Committee Decision and Reasons” issued December 19, 2001, page 16, 17