13 March 2019

Dr. Michael Baker
Rose Family Chair in Medicine UHN
Professor of Medicine University of Toronto

Dear Michael,

As you know, after we brought to the attention of UHN Administration findings, summarized in our recent paper in PLoS One, a need was recognized to assess whether patient safety had been compromised during provision of (then-unlicensed) deferiprone at UHN. As you have requested, we will assist you in this assessment by providing documents, summaries, and any raw data including as requested:

- A clinical summary of the patient's history including within the relevant period of drug administration;
- A one-page summary of clinical and laboratory findings for each interval of deferiprone exposure;
- When relevant, a graph of changes in liver enzymes over the relevant period(s) of deferiprone exposure.
- Any useful additional relevant material as you have requested or may later request to facilitate your review of the patient's situation.
- All our summary findings may, of course, be confirmed in each EMR.

We also write because the circumstances of this important scientific study raise serious ethical considerations. The over-arching question is how deferiprone was prescribed over six years while unlicensed in Canada in more than 40% of regularly-reviewed patients at UHN. **In short, a review of the medical data is not sufficient.** We raise the following considerations, all outlined in the paper.

The circumstances under which unlicensed deferiprone was prescribed for six years at UHN:

Dr. Richard Ward indicated to *Blood* and in a letter to the US FDA that deferiprone was administered in a clinical trial "approved by the REB of the UHN." However, evidence in the EMRs shows that deferiprone was provided through Health Canada's "Special Access Program (SAP)," under which the treating physician must confirm "*conventional therapies have failed, or are unsuitable or unavailable.*" In short, the mechanism under which deferiprone was provided at UHN is unclear.

Reporting to regulatory agencies of relevant findings on UHN patients during deferiprone exposure, as required by law:

After six years of exposure in UHN patients, deferiprone was licensed "primarily on the basis of the Canadian data package", a package of data submitted to Health Canada by UHN physicians and Apotex. [It is the responsibility of the prescribing physician(s) to confirm that all relevant information (including effectiveness, adverse events and deaths) was truthfully submitted before market approval.[1] Since 2015, we have requested this "Canadian data package" and UHN Administration has declined to provide it. In our published paper, we identified a high frequency of SAEs which do not appear to have been reported at all to Health Canada, or to the US FDA.

[1] Failure to supply full and truthful information to a government agency represents fraud.

Drs. Richard Ward and Erik Yeo wrote a letter in 2011 to the US FDA wherein they stated they *"…cannot state how strongly we support [the approval of deferiprone] at the FDA".* Their letter includes a summary of findings that have substantial differences from the data we obtained in the EMR including information about: deferiprone dosing, CBC monitoring, frequency of MRI monitoring, and adverse effects developing during deferiprone exposure.

How was the practice of switching from licensed therapies to unlicensed deferiprone at UHN permitted:

(a) Background of deferiprone in Toronto. Please refer for most of this information to the **letter** from Drs. Olivieri and Gallie to UHN CEO Dr. Smith 20 December 2018 (a copy of which you have already received) in which the following is outlined: twenty years ago, Olivieri and coworkers reported that liver iron concentration, the only parameter correlated with body iron burden, was inadequately controlled in nearly 40% of deferiprone-exposed patients; Apotex abruptly and prematurely terminated the trials threatening "all legal remedies" against Dr. Olivieri and against publication. The ensuing ethical controversy generated great public interest.

(b) Removal of expert care from UHN thalassemia patients in 2009. In 2009, Dr. Olivieri was informed that "corporate UHN thinks you're trouble" and Dr. Malcolm Moore (Director, Medical Oncology & Hematology) removed her as Program Director (offering her inducement of money to accept this dismissal, which Dr. Olivieri refused). Dr. Olivieri was then embroiled in ongoing (ultimately, successful) lawsuits against Apotex and Random House, and could not afford to continue to fight this dismissal by UHN. Also that year "The Alexandra Yeo Chair in Benign Hematology" was established at UHN; Dr. Erik Yeo (Alexandra's widower) was appointed UHN's Director of Benign Hematology. Canadian-trained physicians applied for the position of clinic physician and Dr. Yeo hired Dr. Richard Ward over these applicants. Dr. Richard Ward was a UK citizen and (in 2009), a trainee who had previously worked under UK physicians publicly supportive of deferiprone; lacking a Canadian fellowship, he was awarded at UHN a special license to practice in Canada. Beginning in 2009, an effective program of intimidation and marginalization of Dr. Olivieri and her research team is well documented. There are documented examples of coercion of patients include threats of withdrawal of care if patients enrolled in Dr. Olivieri's research studies, culminating with Dr. Olivieri's long employed Clinical Research Officer quitting abruptly in 2010.

(*c) Notification of UHN administrators and lawyers about deferiprone use at UHN.* Ten years prior to our paper reaching the press, in 2009 the UHN Administration commissioned a "Report" from Dr. Anne Yardumian a former UK colleague of Dr. Ward who had trained, worked and published with Apotex' key opinion leaders, and publicly defended Apotex' actions against Dr. Olivieri. Dr. Yardumian approved the use of deferiprone at UHN. The Yardumian Report, which was relied upon in subsequent communications to Dr. Olivieri[2] became central to the continuing use of deferiprone at UHN over the next five years.

(d) Formal inspection of Dr. Olivieri's UHN data (July 2009) by the US FDA Division of Scientific Investigations' leads to FDA's refusal of deferiprone approval (September 2009). UHN was informed in 2009 that the US FDA had cancelled Apotex' application for market approval of deferiprone after a formal inspection by The FDA Division of Scientific Investigations (DSI) of Dr. Olivieri's data (from the original trials at UHN), sparked by Apotex' incorrect allegations about Dr. Olivieri. The DSI identified inconsistencies between data in Dr. Olivieri's original case report forms and the data Apotex had submitted to the FDA, on

[2] For example, Dr. Charles Chan (Vice-President, Medical Affairs & Quality Care at UHN) wrote to Dr. Olivieri in 2012: "*the appropriateness of the clinical use of deferiprone at UHN has been exhaustively reviewed in the relatively recent past and has been completely validated.*"

UHN patients; the following month, FDA cancelled the scheduled meeting to review Apotex' submission for licensing of deferiprone, "because of the significant concerns raised by the inspection" including these key observations:

> Data submitted by Apotex to FDA compared to original data summaries "raised a number of questions regarding Apotex's criteria for inclusion and exclusion of data … with respect to hepatic iron concentration data" [the primary endpoint of the trial]
>
> (ii) "Specifically, Aotex's data set excluded in their entirety 23 of 63 treated subjects treated subjects.
>
> (iii) "The rationale for exclusion of data was inconsistently applied by Apotex.
>
> (iv) "The inspection of Dr. Olivieri's site (1) revealed discrepancies in the hepatic iron concentrations between Apotex's data listings, and the documents at Dr. Olivieri's site, and ***where source documentation was available, Dr. Olivieri's data appeared to be reliable***; (2) Data Apotex excluded from the 24-month completer analyses may not have been appropriate for exclusion, and (3) Dr. Olivieri had documents at her site that suggested increased hepatic iron and/or hepatic fibrosis with chronic deferiprone therapy, although FDA was not able to verify the source for these values.

As noted by the most prominent Health Research organization in the USA Public Citizen: "Given the lack of data from adequate and well-controlled clinical trials demonstrating the safety and efficacy of deferiprone, as well as serious questions raised by the FDA inspection of the Toronto study, the FDA should reject approval of deferiprone. Approval based on such inadequate data would indeed set a recklessly dangerous precedent for drugs reviewed under an accelerated approval process in the future." Despite many of these public documents being available to UHN administrators, administration of deferiprone at UHN continued to escalate, as our paper indicates.

Apparently undisclosed Conflicts of Interest by UHN, Dr. Ward and Dr. Yeo:

While launching new lawsuits against Dr. Olivieri from 2008, Apotex was in 2010 providing substantial funding to the thalassemia program at UHN. In addition, a donation of between "$1 million and $5 million" is recorded from UHN by Barry Sherman, now-deceased CEO of Apotex, to UHN. Funding from Apotex to UHN included unrestricted educational grants (*although name brand firms are now prevented from providing these grants, as a generic company, Apotex had no such restrictions*). UHN Director of Research Dr. Christopher Paige denied the provision of Apotex funding when this issue was discussed with him in December 2011 by Dr. Olivieri. However, it was confirmed in a Freedom of Information search which also revealed correspondence between Apotex and Dr. Ward about obtaining market approval of deferiprone at Health Canada, as well as requests to Apotex from Dr. Ward for increasing amounts of funding.[3]

What information was given to patients switched from licensed therapies to deferiprone:

Our publication indicates that many of the patients switched from first line therapy to deferiprone suffered serious harms. Did the patients switched to deferiprone understand that they were being switched from

---

[3] The Royal College of Physicians of Canada notes that such conflicts of interest are problematic: "Institutions may receive industry funding for an important part of their activities. They may be financially dependent on these sponsors for funding some aspects of the health care they provide, social activities for patients and staff, academic chairs and/or research or educational activities. Decisions about which drugs to prescribe, research priorities, allocation of research space, assigning research mandates, promoting specific research agendas, and providing priority access to patients within a health care institution, could be (or could be perceived to be) influenced by these financial interests. An institutional COI can also exist when a company or individual donates a significant amount of money to an institution, and when research or decisions within the institution may affect the financial interests of that company or individual. The concern would be that the institution has an interest in keeping the donor satisfied and happy."[3]

treatment (deferiprone and deferasirox) whose safety and efficacy had been established and licensed by regulators, including Health Canada, to an unlicensed drug (deferiprone)? How were the medical outcomes (sustained elevations in liver iron concentration to levels associated with premature death, new diabetes mellitus, liver dysfunction) explained to patients and families treated with deferiprone? How was the death of a young mother (*a patient who had expressed a desire to continue standard licensed therapy, but who was prescribed deferiprone instead*) explained to her family and children? What did these patients understand about the literature (*discussed in our paper*) about the published effectiveness of reduction of liver or heart iron during deferiprone monotherapy? Were patients informed in particular that all regulatory agencies mandate weekly monitoring for deferiprone-induced agranulocytosis and that less monitoring has led to many deaths? Was the patient repeatedly exposed to deferiprone after developing life-threatening agranulocytosis informed that such re-exposure is contra-indicated?

Ongoing obstructions to thalassemia research at UHN by Dr. Ward threaten academic freedom:

The REB-approved study by Drs. John Dick and Nancy Olivieri, which builds on 30 years of fetal hemoglobin research, has been prevented from going forward by Dr. Ward indicating that Dr. Olivieri is not in the "circle of care." However, the Tri-Council statement emphasizes that individuals in the circle of care are less well placed to consent patients than are those outside the circle of care. Meetings of Drs. Dick, Olivieri and Gallie with UHN administrators including Dr. Wouters have failed to resolve this problem. To date, important REB approved research continues to be blocked and the academic freedom of Drs. Olivieri and Dick continues to be violated.

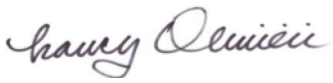
In SUMMARY, a review of the medical data is not sufficient:

We state in our published paper *"Six years of prescription of an unlicensed drug to one-third of patients in UHN, while serious sustained toxicities were recorded without resumption of licensed therapy, suggests a need for review of standards of clinical practice, protection of patient safety, processes of patient consent, and other ethical and administrative issues at the UHN Canada's largest research institute."*

Thank you for undertaking this important work.

Respectfully submitted,

Brenda L. Gallie, MD, FRCSC, CM, OOnt
Head, Retinoblastoma Programs,
Hospital for Sick Children and Alberta Children's Hospital
Associate Scientist, TECHNA Institute, UHN
Professor, Ophthalmology, Medical Biophysics,
Molecular Genetics, University of Toronto
555 University Ave, Toronto M5G 1X8
brenda@gallie.ca



Nancy F. Olivieri, MD, MA, FRCPC
Professor, Pediatrics, Medicine and Public Health Sciences,
University of Toronto, Canada;
Senior Scientist, Toronto General Hospital, UHN
200 Elizabeth Street, EN 13-222,
Toronto, Ontario Canada M5G 2C4
nancy@hemoglobal.org