5 March 2019

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

Dear Michael,

Re: Response to Dr. Richard Ward's letter regarding Reviewers for the Inquiry into Patient Care, UHN, 2019

Thank you for sending us Richard Ward's recent communications. We are delighted to learn that Dr. Ward is eager to have outcomes of patients in the Red Cell Clinic reviewed. We hope that this Review will assist in a new opportunity, as noted by Dr. Gallie, "to actualize the UHN's commitment to 'reduce preventable patient harm to zero.'

Dr. Ward suggested the following individuals:

Drs. Janet Kwiatkowski and Alan Cohen of Children's Hospital of Philadelphia

Our reply: It is public knowledge that Drs. Kwiatkowski and Dr. Cohen, both enthusiastic proponents of deferiprone, have enjoyed close ties to and financial support from Apotex for more than 25 years. Dr. Kwiatkowski continues to advocate publicly for the widespread prescribing of deferiprone. As chair of the Cooley's Anemia Foundation Medical Advisory Board, Dr. Kwiatkowski oversaw the 2017 awarding of a "Cooley's Anemia Foundation Humanitarian Award" to two full-time Apotex employees, neither of whom had conducted original research on deferiprone.

In 1996, after Apotex fired Dr. Olivieri, and Dr. Gary Brittenham resigned in protest, Dr. Cohen took over their scientific leadership of the Apotex-paid "safety" study. That study reported (in 1998, *before* the drug was licensed in Europe) that deferiprone-induced liver abnormalities were transient. Dr. Cohen later acknowledged (in 2003 *after* European licensing had been obtained) these liver abnormalities to be persistent, and significant (as confirmed in our PLoS One paper).

Dr. Antonio Piga

Our reply: Dr. Piga has had financial support from Apotex and its employees over 25 years, and is a zealous enthusiastic for deferiprone use. In Europe, the drug is licensed for third-line use only, as in all jurisdictions worldwide. Dr. Piga holds a patent with the President of Apotex to profit from the "cardiac superiority" of deferiprone.[1] Dr. Ward claims he not "worked with [Piga] previously." However, we note that in October 2018, in a Toronto conference with Dr. Ward, Dr. Piga was invited to lecture to UHN patients about chelating therapy.

Dr. Ellis Neufeld

Our reply: Dr. Ward co-testified with Dr. Neufeld (on behalf of Apotex) at a FDA Advisory Meeting about deferiprone in 2011. Dr. Ward and Dr. Neufeld were retained as part of long-term, concerted efforts with Apotex to persuade the FDA to license deferiprone in 2011. The FDA had recognized irregularities in the data submitted by Apotex and refused approval in 2009. At the 2011 FDA Advisory Meeting, Drs. Ward and Neufeld, on behalf of Apotex, strongly endorsed

1 Although the "cardiac superiority" of deferiprone has been promoted by Drs. Piga, Kwiatkowski, Neufeld and Coates, the data Apotex submitted to FDA to support superior 'cardio-protection' by deferiprone was judged by the FDA to be inadequate to establish any 'cardio-protective' effect of deferiprone.

FDA approval of deferiprone.[2] A strong proponent of deferiprone use for American patients,[3] Dr. Neufeld eventually left the thalassemia field for managerial work.

Dr. Thomas Coates

Our reply: Dr. Thomas Coates has well-documented established ties to Apotex over many years. Dr. Coates worked very closely with Apotex and its consultants; a full-time Apotex employee, Dr. Vasili Berdoukas, previously worked with Dr. Coates in the hemoglobinopathy clinic at LA Children's. Dr. Coates is an ardent proponent of the widespread use of deferiprone in the USA.

Conflict of Interest for Apotex-supported Reviewers:

We conclude that these individuals suggested by Dr. Ward are not appropriate to participate in an unbiased Inquiry because of documented conflicts of interest, lack of experience and knowledge, and/or personal allegiances (for some all three).

UHN is already in a difficult position with evidence (obtained through Freedom of Information) that Apotex supplied money to Dr. Ward and the Red Cell Program (whether, and when, declared is not clear) while Dr. Ward was prescribing the company's unlicensed drug, and made contemporaneous donations to UHN up to $5 million. As you know, with respect to Gideon Koren at SickKids, inquiries involving various conflicted individuals failed to address real issues, so ultimately external extended reviews were required**.**

As evident from our many efforts to bring these issues to the attention of the highest levels of UHN over 10 years, before our publication became public, we continue to strive to assist the UHN to address these seemingly complex issues, and live up to the UHN publicly stated goals for safety. As Dr. Gallie noted more than two years ago: "The best for all (for a bright safe future world) would be an inquiry with full disclosure when the UHN has both the conflicts of interest and the patient harm addressed." This cannot be achieved through the appointment of Reviewers paid by or with allegiances to Apotex or within Apotex' extensive network.

Dr. Kate Ryan

Our reply: Dr. Kate Ryan does not appear to have direct conflict of interest concerning Apotex, but there are several reasons why she is also inappropriate for the up-coming review of the Red Cell Program.

i. Dr. Ryan is a close associate of, and co-author, with Dr. Anne Yardumian, a colleague of Dr. Ward. In 2009, Dr. Yardumian (with a nurse working in sickle cell disease), undertook the production of a Report (The "Yardumian Report") commissioned by UHN Administration in response to Dr. Olivieri having raised concerns about Dr. Ward's then-emerging widespread use of unlicensed deferiprone. Dr. Yardumian has trained, worked and published with Apotex' key opinion leaders, and publicly defended Apotex' years of actions against Dr. Olivieri. Not surprisingly, the "Yardumian Report" unequivocally approved Dr. Ward's switching of UHN patients from licensed therapies to deferiprone, then unlicensed in Canada. Responding to the "Yardumian Report," UHN patients and others indicated their views of its flaws: that Yardumian and her colleague possessed conflicts of interest, inadequate expertise, and did not interview many patients who had requested interviews. The UHN nonetheless endorsed the Yardumian Report, which supported the continuing use of deferiprone at UHN. Senior

2 Dr. Ward had written previously to the FDA that Dr. Ward: "…cannot state how strongly [he] supports the market approval of deferiprone," adding to his letter findings in Toronto patients that are inconsistent with data we identified in the records of Toronto patients.

3 The US FDA refused first-line approval, and approved deferiprone as third-line therapy only, because of a "failure to provide answers to [the FDA's] questions on efficacy and safety." FDA's approval of deferiprone, the agency's first approval not to require evidence from a "adequate well-controlled clinical trial or a validated surrogate marker," has been described as a "recklessly dangerous precedent." The FDA drug monograph confirms that "no controlled trials of deferiprone demonstrate a direct treatment benefit." All references provided in our PLoS ONE paper.

UHN administration subsequently relied on the Yardumian Report to dismiss concerns raised by Dr. Olivieri in official UHN channels over the next decade.

ii. Dr. Ryan co-authored an "Editorial/Writing Group" for a non-peer reviewed document titled: *Standards for the Clinical Care of Children and Adults with Thalassaemia in the UK, 3rd Edition 2016*, co-authored by many proponents of deferiprone. For example, Dr. Yardumian, mentioned above, is the Group's lead author. Dr. Ryan is the fourth of seven authors. Dr. Ward is acknowledged for his work on these 'Standards', a finding inconsistent with Ward's statement to you that *"I have no personal or professional connection with [Dr. Ryan])"*. The 'Standards' were produced with support of The UK Thalassemia Society, a "patient" organization that has for decades been funded robustly by Apotex.[4] Not surprising, these 'Standards' contain statements and recommendations consistent with Apotex recommendations but not evidence-based, including those which contradict both the findings of the 2013 Cochrane Systematic Review of deferiprone and published regulatory guidelines.[5] To achieve a safe environment for patients in the UHN, reliance on evidence-based, industry-independent literature is important to the upcoming independent, patient safety Inquiry. In our view, Dr. Ryan may be under-informed with respect to the industry-independent literature about deferiprone.

iii. Despite co-authoring these 'Standards', Dr. Ryan is not an established figure in thalassemia care. Manchester where she works is not a well-known UK center for thalassemia care. Dr. Ryan has not published a body of work in thalassemia. Indeed, Dr. Ryan has authored exactly *three* academic publications from 2010 to 2018, two in thalassemia, with Dr. David Rees a co-author in one.

iv. Dr. Ryan is being proposed as a reviewer in an Inquiry that is charged to examine the quality of patient care at UHN. Dr. Ryan may find herself conflicted if the Inquiry finds evidence that is critical of Dr. Ward, since he has been supported and promoted by Dr. Ryan's closest colleagues, including Anne Yardumian whose "Yardumian Report" was the primary enabler of Dr. Ward's ongoing prescribing of unlicensed deferiprone at UHN.

Olivieri/Gallie suggestion for independent reviewer

Professor David Rees

Our suggestion of Professor David Rees stems from his work in thalassemia, and his research publications in sickle cell disease and thalassemia. Professor David Rees trained in thalassemia under world leaders, Professors David Weatherall and John Clegg. He has worked overseas with large numbers of patients with thalassemia. While Professor Rees is not currently primarily working in thalassemia at Kings', he possesses substantial knowledge, experience, and an established track record of research in thalassemia. Professor Rees' qualifications stand in contrast to those of either Dr. Ryan or Dr. Ward himself.

To the best of our understanding, Dr. Ward did not undergo any training toward a Fellowship of the Royal College of Physicians and Surgeons of Canada, nor does he have a formal record of Canadian training in either internal medicine or hematology. Although well-qualified Canadians applied for this position, Dr. Ward was selected in 2009 to head the Red Cell Program, and required a "special license" to practice medicine at UHN. Dr. Ward has no significant publication record in any field, including thalassemia, during his ten years at UHN.

4 More than any other organization worldwide, over 30 years the UK Thalassemia Society has encouraged, supported, upheld and promoted Apotex, its employees, and its paid key opinion leaders in all issues relevant to deferiprone.

5 As recorded in our PLoS ONE paper, the Cochrane Systematic Review summarized decades of deferiprone literature as "disparate findings" in "small series of patients." The Cochrane Review judged most deferiprone studies to be "severely compromised" including by faulty trial design, skewed data, questionable randomization processes, and failures to report baseline data; it noted that long-term outcomes were measured in few trials and, when reported, were "limited and inconclusive." See also footnote 3.

New suggestion for Independent Reviewer:

We recognize, however, that it will be difficult to find someone acceptable to both Dr. Ward and ourselves, not least because Dr. Ward has recommended exclusively Apotex-allied individuals.

We suggest Dr. Elliott Vichinsky of the Benioff Children's Hospital UCSF to assist Dr. Baker in this Inquiry. Dr. Vichinsky is the leading care provider and investigator in thalassemia today. No one outranks what he possesses in terms of quality of care, experience and depth of knowledge in thalassemia. This year's Distinguished Career Awardee of the ASPHO, Dr. Vichinsky has contributed to scientific and clinical work in thalassemia and sickle cell disease for over 30 years, during which he has furthered understanding of disease processes and published significant hypothesis-driven studies defining guidelines for the optimal management of thalassemia. He is also a highly ethical person, fair, honest and self-possessed, and highly familiar with challenges related to hospital administration.

Dr. Vichinsky and I have been co-authors on several papers over years. However, this co-authorship (with me) is also true of Drs. Kwiatkowski, Cohen and Neufeld, whose names Dr. Ward had no trouble in providing. Dr. Vichinsky is not allied with Apotex; however, he has conducted studies with Apotex in a very rare iron loading disease unrelated to the present concern for patients at UHN.

Sincerely,

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