UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

TARO PHARMACEUTICALS U.S.A., INC.,
Petitioner,

v.

APOTEX TECHNOLOGIES, INC.,
Patent Owner.

Case IPR2017-01446
U.S. Patent No. 7,049,328 B2

Title: USE FOR DEFERIPRONE

**SECOND DECLARATION OF DUDLEY J. PENNELL, M.D.,
IN SUPPORT OF PATENT OWNER'S RESPONSE**

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I, Dudley J. Pennell, M.D., declare as follows:

I. INTRODUCTION, BACKGROUND, AND QUALIFICATIONS

1. My compensation, background, and qualifications have remained the same since the submission of my Declaration in Support of Patent Owner's Preliminary Response (Ex. 2003). (Ex. 2003 at 1-3.)

II. LEGAL STANDARDS

2. My understanding of the legal standards for anticipation and obviousness are the same as set forth in my Original Declaration. (Ex. 2003 at 3-5.)

III. BACKGROUND OF THE TECHNOLOGY

A. There Were No Reliable Methods to Quantify and Correlate Cardiac Iron Content with Cardiac Disease at the Time of the Invention

3. As discussed in my Declaration (Ex. 2003), there was a misguided belief that a liver iron concentration ("LIC") >80 µmol of iron per gram of liver ("µmol/g"), wet weight (or >15 mg/g, dry weight), was associated with an increased risk of heart disease in blood transfusion dependent patients. (Ex. 2003 at 7-8; *see* e.g., Ex. 1012 at 921; *see also* Ex. 2011 at 419; Ex. 1017 at 565.)

4. In addition to my own experiments showing that LIC is not reflective of, and in no way predicts cardiac iron content (Ex. 2007), a study by Berdoukas

(Ex. 2022)[1] directly challenged and disproved Olivieri and Brittenham's proposed association between cardiac iron levels and LIC. (Ex. 2022 at 685-686.) The study included 58 transfusion-dependent patients stratified into three groups:

- Group I included patients with LIC <7 mg/g dry weight;
- Group II included patients with LIC between 7 mg/g dry weight and 15 mg/g dry weight; and
- Group III included patients with LIC >15 mg/g dry weight.

(Ex. 2022 at 685, Table 1.)

5. All groups were evaluated for cardiac dysfunction with multiple uptake gated acquisition ("MUGA") scans. (Ex. 2022 at 685.) The empirical results showed that thalassemia ("TM") patients having LIC >15 mg/g, dry weight, and even as high as 62 mg/g, dry weight, exhibited the same cardiac function as TM patients having LIC of 6.8 mg/g, dry weight. (Ex. 2022 at 685, Table 1.) Further, the study demonstrated that there was no statistical difference in the cardiac function of TM patients averaging an LIC of 32.4 mg/g, 10.4 mg/g, and 4.2 mg/g, dry weight. (Ex. 2022 at 685-686, Table 1.) Thus, a POSA can only conclude that a LIC >15 mg/g, dry weight, cannot be associated with iron overload in the heart, let alone indicative of cardiac disease. *See* e.g., Ex. 2006 at 2973; Ex.

[1] V. Berdoukas *et al.* "Lack of correlation between iron overload cardiac dysfunction and needle liver biopsy iron concentration," *Haematologica* *90*(5):685-6 (2005) (Ex. 2022).

2027[2] at 100; Ex. 2028[3] at 272; Ex. 2029[4] at 2; Ex. 2030[5] at 214. Berdoukas also highlights that in "15 patients with a LIC in the range in which one might expect serious problems from iron overload, only one had an abnormal resting LVEF and only two had a significant reduction in their ΔLVEF." (Ex. 2022 at 686.)

6. In my Declaration, I also commented that serum ferritin ("SF") levels are not indicative of cardiac iron content. (Ex. 2003 at ¶¶ 26, 51.) To be clear, it has been well known since 1976 that SF levels are not reflective of parenchymal iron content (i.e., the iron content of organs such as the heart and liver). (Ex. 2031[6] at 46; Ex. 2032[7] at 333-4.)

7. In my Declaration, I further commented on the state of magnetic resonance imaging ("MRI") technology, and specifically that, as of the 1990s, MRI

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[2] A. Aessopos *et al.* "The heart in transfusion dependent homozygous thalassaemia today – prediction, prevention and management," *Eur. J. Haematology 80*:93-106 (2008) (Ex. 2027).
[3] N. Koonrungsesomboon *et al.* "Early detection of cardiac involvement in thalassemia: From bench to bedside perspective," *World J. Cardiol. 5*(8):270-279 (2013) (Ex. 2028).
[4] A. Aessopos *et al.* "Prevention of Cardiomyopathy in Transfusion-Dependent Homozygous Thalassaemia Today and the Role of Cardiac Magnetic Resonance Imaging," *Advance in Hematology* Article ID 964897:1-4 (2009) (Ex. 2029).
[5] S. Lekawanvijit *et al.* "Iron overload thalassemic cardiomyopathy: Iron status assessment and mechanisms of mechanical and electrical disturbance due to iron toxicity," *Can. J. Cardiol. 25*(4):213-218 (2009) (Ex. 2030).
[6] DL Johnston *et al.* "Assessment of tissue iron overload by nuclear magnetic resonance imaging," *Am. J. Med. 87*(1):40-7 (1989) (Ex. 2031).
[7] WH Crosby "Editorial: Serum ferritin fails to indicate hemochromatosis--nothing gold can stay," *N. Engl. J. Med. 294*(6):333-4 (1976) (Ex. 2032).

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