IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor: Jiang Application No.: 13/597,884 Filed: August 29, 2012 Title: Levothyroxine Formulations	Art Unit: 1627 Examiner: Kara R. McMillian Docket No.: FKA01_007_US

DECLARATION UNDER 37 C.F.R. § 1.132 OF ARUNYA USAYAPANT

Commissioner for Patents
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I, Arunya Usayapant do hereby declare as follows:

1. I am one of the named inventors on the present patent application.

2. I received a Ph.D. degree in Pharmaceutical Sciences in 1991 from Northeast Louisiana University in Monroe, LA, and a B.S. degree in Pharmacy in 1982 from Chulalongkorn Mahawitthayalai in Bangkok, Thailand.

3. I have over 15 years of formulation and development experience in the pharmaceutical industry. Since 2007, I have been employed at Fresenius Kabi USA (formerly APP Pharmaceuticals), which is the assignee of the present patent application, in the following roles: Senior Manager (2013-present), Manager (2008-2013), and Principal Scientist (2007-2008). Prior to my current employer, I was employed as a Senior Principal Scientist at Morton Grove Pharmaceuticals (now Wockhardt USA) in Morton Grove, IL, from 2004-2006; as a Senior Scientist at Wyeth Consumer Healthcare in Richmond, VA, from 1998-2004; as an Assistant Professor at Chicago College of Pharmacy in Downers Grove, IL, from 1992-1998; and as an Assistant Professor at Northeast Louisiana University from 1991-1992.

4. I am aware of the general knowledge available in the field of lyophilized pharmaceutical products and of the skill level of the ordinary artisan in the field of lyophilized pharmaceutical products as it exists today and as it existed at the time of the invention of the subject matter claimed in the present patent application.

5. I understand that the currently pending claims are directed to a lyophilized solid composition containing 100 µg, 200 µg, or 500 µg levothyroxine sodium, a phosphate buffer, and from 2 to 4 mg mannitol or, more specifically, about 3 mg mannitol.

6. I have reviewed the Office Action dated September 8, 2014, and the references cited therein, namely: 1) Bedford Laboratories, "Levothyroxine Sodium For Injection", 2003 ("Bedford"); 2) Collier et al., "Influence of Formulation and Processing Factors on Stability of Levothyroxine Sodium Pentahydrate," *AAPS PharmSciTech., 11(2)*: 818-825 (2010) ("Collier"); 3) Baheti et al., "Excipients Used in Lyophilization of Small Molecules," *J. Excip. Food Chem., 1(1)*: 41-54 (2010) ("Baheti"); and 4) Kim et al., "The Physical State of Mannitol after Freeze-Drying: Effects of Mannitol Concentration, Freezing Rate, and a Noncrystallizing Cosolute," *J. Pharm. Sci., 87(8)*: 931-935 (1998) ("Kim").

7. A lyophilized solid has a different physical structure and reactivity than a solid that is dissolved in a liquid or than a solid that is compressed to form a tablet; thus, the reactivity of a solid in a liquid and a lyophilized solid cannot be directly compared. In my opinion, a person of ordinary skill in the art would not consider a reference directed to levothyroxine stability in water or in a compressed tablet to be relevant to the development of a stable lyophilized solid composition.

8. Prior to the present invention, I was unaware of any publication or general knowledge in the art that disclosed or otherwise suggested that the lyophilized pharmaceutical products comprising 200 µg or 500 µg levothyroxine sodium and at least 10 mg mannitol – which had been marketed in the United States since at least 1971 as grandfathered products – had undesirable impurity profiles.

9. The results described in the specification of the present patent application demonstrate that reduced amounts of the impurity liothyronine (T3) are formed following storage for1-3 months at 40 °C or for 2-4 weeks at 55 °C of lyophilized solid compositions comprising 100 µg levothyroxine sodium and 2 mg, 3 mg, or 4 mg mannitol as compared to conventional lyophilized solid composition comprising 100 µg levothyroxine sodium and 10 mg mannitol (see paragraphs 0033-0036 and Table 1 of the specification).

10. The results described in the specification of the present patent application also demonstrate that reduced amounts of liothyronine are formed following storage for 3-6 months at 40 °C or for 12-18 months at 25 °C of lyophilized solid compositions comprising 100 µg, 200 µg, or 500 µg levothyroxine sodium and 3 mg mannitol (hereinafter referred to as "compositions of the invention" or simply "invention") as compared to conventional lyophilized solid compositions comprising 10 mg mannitol and 100 µg, 200 µg, or 500 µg levothyroxine sodium (hereinafter referred to as the "conventional compositions" or simply "conventional") (see paragraphs 0037-0049, Tables 2-3, and Figs. 2-3 of the specification).

11. The stability experiments of the compositions of the invention were extended to 24 months at 25 °C. The stability experiments of the conventional compositions were terminated at 18 months, since the increasing amounts of liothyronine impurities were indicative of unstable products. The results of the extended stability experiments are described herein as follows.

12. The amount of liothyronine impurity present following storage for 24 months at 25 °C of the compositions of the invention comprising 100 µg, 200 µg, or 500 µg levothyroxine sodium was 0.13% (see Exhibit A attached hereto at Figs. 1A-1C), which represented a minimal (8%) increase in the amount of liothyronine impurity over the 24 month storage period. In contrast, the amounts of liothyronine impurity present following storage for 18 months at 25 °C of conventional compositions comprising 100 µg, 200 µg, or 500 µg levothyroxine sodium were 0.25%, 0.25%, and 0.18%, respectively (see Exhibit A at

Figs. 1A-1C), which represented a substantial (6%-47%) increase in the amount of liothyronine impurity over the 18 month storage period.

13. In my opinion, the results described in the specification of the present application and as supported by Figs. 1A-1C in Exhibit A attached hereto are unexpected in view of the combination of cited references and the general knowledge in the art, since I was unaware of any study demonstrating that reducing the amount of mannitol would have affected levels of liothyronine impurity in a lyophilized solid levothyroxine composition.

14. In 2011, the United States Food and Drug Administration ("FDA") approved Fresenius Kabi USA's New Drug Application (NDA) 202231 for Levothyroxine Sodium for Injection containing 100 µg, 200 µg, or 500 µg levothyroxine sodium, 3 mg mannitol, and a phosphate buffer, which correspond to compositions of the invention. Prior to 2011, Fresenius Kabi USA manufactured and sold a grandfathered Levothyroxine Sodium for Injection product containing 200 µg or 500 µg levothyroxine sodium, 10 mg mannitol, and a phosphate buffer (hereinafter referred to as "compositions of the prior art" or simply "prior art"). The prior art compositions previously sold by Fresenius Kabi USA are substantially similar to the compositions described in Bedford.

15. I have reviewed stability testing summaries compiled at Fresenius Kabi USA of commercial-scale preparations of compositions of the invention (200 µg/vial levothyroxine sodium) and compositions of the prior art (200 µg/vial levothyroxine sodium). Summaries of the stability assay and certain test results are described herein as follows.

16. All vials were stored at 25±2 °C, 60± 5% relative humidity in an inverted position for 18 or 24 months. Prior to storage and at the end of the storage period, the amount of levothyroxine present in each vial was calculated by a high-performance liquid chromatography method. After 18 months, the prior art compositions exhibited, on average, a loss of approximately 7.7% of the initial amount of levothyroxine. In contrast, the compositions of the invention did not exhibit, on average, any loss of levothyroxine (see

Exhibit A at Fig. 2). Similarly, at 24 months, the prior art compositions exhibited a loss of approximately 8.8% of the initial amount of levothyroxine, whereas the compositions of the invention still did not exhibit any loss of levothyroxine (see Exhibit B at Fig. 2).

17. The current Fresenius Kabi USA Levothyroxine Sodium for Injection product marketed under NDA 202231 (invention) has a shelf-life of 24 months, whereas the previous Fresenius Kabi USA Levothyroxine Sodium for Injection marketed as a grandfathered product (prior art) had a shelf-life of 18 months.

18. Based upon my experience, I believe that the FDA would not have approved an NDA for a conventional lyophilized solid composition comprising 200 µg or 500 µg levothyroxine sodium and 10 mg mannitol, such as the grandfathered Fresenius Kabi USA or Bedford product. In my opinion, the FDA would have considered the increased impurities and decreased potency following storage problematic, especially for a drug product containing a highly potent active pharmaceutical ingredient, such as levothyroxine.

19. In my opinion, the superior stability and extended shelf-life of the compositions of the invention as compared to the prior art compositions are unexpected in view of the combination of cited references and the general knowledge in the art, as I was unaware of any study suggesting that reducing the amount of mannitol in a lyophilized solid composition would have positively affected levothyroxine potency following storage, much less extend the shelf-life of a commercial product.

20. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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