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

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We, Zhi-Qiang Jiang, Arunya Usayapant, and George Monen, declare as follows:

1. We are the inventors of the subject matter claimed in the above-identified U.S. Patent Application.

2. We have assigned the above-identified U.S. Patent Application to Fresenius Kabi USA, LLC.

3. At the time of the invention of the subject matter claimed in the above-identified U.S. Patent Application, we were employees of Fresenius Kabi USA, LLC and continue to be employees of Fresenius Kabi USA, LLC on the date of our signatures below.

4. When we performed the research leading to the filing of the instant patent application, we were unaware of any study showing that different excipient amounts would have significant effect on levothyroxine stability in lyophilized solids, instead believing that excipient type was most important to levothyroxine stability.

5. When performing this research, we were unexpectedly surprised by the type of stability results obtained from the data presented in Tables 1-3 and Figures 2 and 3 of our patent application. The tables and figures show that at the higher 10 mg mannitol level, increasing amounts of mannitol in relation to levothyroxine adversely affected levothyroxine stability in a somewhat linear manner, while at the lower 3 mg mannitol level, a significant and wholly unexpected departure from this degradation linearity was observed over the attempted levothyroxine concentrations. Thus, after seeing the degradation trend at the higher mannitol concentration, the break from linearity and substantial flattening due to the stability uniformity observed at the lower mannitol concentration was surprising and much greater than expected.

6. We also were unexpectedly surprised by the difference in the degree of levothyroxine degradation when the high and low mannitol concentrations were compared. From the low mannitol concentration stability results of Table 2, the %T3 increased from 0.12 % [(0.12+0.12+0.12)/3] to approximately 0.131 % [(0.13+0.13+0.133)/3] over a 3 month period when all T3 percentages at the different levothyroxine concentrations were averaged. This represented an approximate 9% degradation over the 3 month period at 40° C [(0.131-0.12)/0.12*100]. In contrast, from the high mannitol concentration stability results of Table 3, the %T3 increased from 0.173 % [(0.17+0.18+0.17)/3] to approximately 0.286 % [(0.403+0.253+0.203)/3] over a 3 month period when all T3 percentages at the different levothyroxine concentrations were averaged. This represented an approximate 65% degradation over the 3 month period at 40° C [(0.286-0.173)/0.173*100]. A greater than 7-fold increase in levothyroxine degradation at the higher mannitol concentrations in relation to the lower mannitol ranges was surprising and much greater than expected.

7. We also were unexpectedly surprised to find that similar levothyroxine stability was observed at the lower mannitol concentration for each levothyroxine concentration. In view of the relatively wide separations between the stability of the higher mannitol concentration samples at each levothyroxine concentration, the uniformity of the stability achieved at the lower mannitol concentration (substantially

levothyroxine concentration independent) also was unexpected. As discussed in paragraph 35 of the application, the stability of the higher mannitol concentration samples varied by approximately 90% over a 3 month period, while the lower mannitol concentration samples varied by approximately 6% over the 3 month period. The surprising difference in the relatively large amount of stability variance at the high mannitol concentration in relation to the substantial lack of stability variance at the low mannitol concentration observed in Figures 2 and 3 of the patent application was unexpected. A fifteen-fold decrease in stability variance at the lower mannitol concentration in relation to the higher mannitol concentration was surprising and much greater than expected.

8. A lyophilized solid has a different physical structure and reactivity than a solid that is dissolved in liquid or than a solid that is compressed to form a tablet. A lyophilized solid is extremely dry, as during the lyophilizing process water is frozen and removed under high vacuum from the solid. Thus, the reactivity of a solid in a liquid in comparison to a lyophilized solid cannot be directly compared. When a lyophilized solid is formed, the vacuum removal of the frozen water and other volatile solvents leaves gaps or pores in the resulting solid. This is very different from a solid that is tightly compressed to form a tablet by the substantial removal of gaps or pores. Thus, the reactivity of a solid that is compressed to form a tablet in comparison to a lyophilized solid cannot be directly compared. Furthermore, as a lyophilized solid is formed from the removal of solvent directly, the lyophilized solid also has a different physical structure than would result from crystallization or precipitation of the solid from the solvent. Lyophilized solids have unique physical structures and reactivities in comparison to other solid forms.

9. Any document or study that discusses levothyroxine stability in water or in a compressed tablet would not be referenced or helpful for developing a lyophilized formulation of levothyroxine.

10. We have reviewed and understand the contents of the cited documents 1) U.S. Patent No. 5,955,105 to Mitra et al. (*Mitra*); 2) Bedford Laboratories,

"Levothyroxine Sodium For Injection", 2003 (*Bedford*); and 3) Collier et al., "Influence of Formulation and Processing Factors on Stability of Levothyroxine Sodium Pentahydrate", *APPS PharmSiTech* 11(2), 2010, 818-825 (*Collier*).

11. It is our conclusion that these documents cited against the claims of our patent application fail to teach lyophilized solid compositions including the claimed critical relative amounts of levothyroxine sodium and mannitol and that direct comparison of the presently claimed inventions to the closest cited art is not possible. These cited documents also are silent regarding how a change in the amount of excipient in relation to the amount of levothyroxine might affect the stability of the levothyroxine.

12. *Mitra* discloses tablets containing levothyroxine sodium and one or more excipients. The ratio of levothyroxine sodium to mannitol in the tablets may be from 1:0 to 1:2,500. *Mitra* fails to teach whether the presence, absence or concentration of mannitol has any effect on the stability of levothyroxine in the tablets. *Mitra* does not disclose or suggest our claimed critical relative amounts of levothyroxine sodium and mannitol in a lyophilized solid. *Mitra* also is silent regarding levothyroxine stability in lyophilized solids.

13. *Bedford* discloses a solid composition for use in forming injectable formulations of levothyroxine sodium. The amount of levothyroxine sodium described in Bedford is either 200 or 500 µg, and the amount of mannitol is 10 mg (page 1, 3rd paragraph). *Bedford* does not disclose or suggest our claimed critical relative amounts of levothyroxine sodium and mannitol in a lyophilized solid. *Bedford* also is silent regarding levothyroxine stability in lyophilized solids.

14. *Collier* discloses that crospovidone, povidone, and sodium laurel sulfate caused a greater than 80% degradation of levothyroxine sodium in the presence of moisture in selected 1:1 or 1:10 ratios and should be avoided. (Collier, p. 823 & Table 1). *Collier* also discloses that when in water a 1:10 ratio of levothyroxine sodium and mannitol powders showed a close to 50% degradation of the levothyroxine sodium after

28 days. (Collier, p. 822 & Table 1). Other compounds showing similar degradation as mannitol in the hands of *Collier* were microcrystalline cellulose, and confectioner's sugar. *Collier* also discloses that when in water colloidal silicon dioxide, magnesium stearate, acacia, lactose monohydrate, croscarmellose sodium, corn starch, and sodium starch glycolate in selected ratios of 1:1 or 1:100 showed a less than 50% degradation of the levothyroxine sodium after 28 days. (Collier, p. 822 & Table 1). *Collier* teaches that the preferred excipients for use with levothyroxine in water are colloidal silicon dioxide, magnesium stearate, acacia, lactose monohydrate, croscarmellose sodium, corn starch, and sodium starch glycolate. Thus, *Collier* does not disclose our claimed critical relative amounts of levothyroxine sodium and mannitol of Applicants' claims in a lyophilized solid. *Collier* also is silent regarding levothyroxine stability in lyophilized solids.

15. In the development of our formulation, we initially thought the *Bedford* formulation (200 or 500 µg/vial Levothyroxine with 10 mg of mannitol and tribasic sodium phosphate) would have the desired stability. Our first "lab batch" made in accord with *Bedford* included 500 µg per vial of levothyroxine sodium and appeared promising. Based on this data from this lab batch trial, we expected that results would be similar for 100 or 200 µg per vial of levothyroxine. With the data in hand for the lab batches, we had a high degree of confidence and decided to develop full scale "commercial batches" of levothyroxine/mannitol. Commercial batches are approximately 100 times the amount of a "lab batch" and are substantially more expensive to make. Each commercial batch used 10 mg of mannitol with varying amounts of levothyroxine sodium (100, 200, or 500 µg/vial).

16. Unexpectedly, all three "commercial batches" including 10 mg of mannitol with varying amounts of levothyroxine (100, 200, or 500 µg/vial) were unacceptable. The impurity profiles of these batches were too high. In our experience, a high impurity profile suggests that the drug would not be safe or effective. Additionally, the high impurity profiles may result in the Federal Drug Administration ("FDA") having issues in providing approval for commercial sale of the drug. In fact, the FDA commented that

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