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 LEONARD J. CHYALL

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

I, Leonard J. Chyall do hereby declare as follows:

1. I received a Ph.D. degree in Chemistry in 1991 from the University of Minnesota in Minneapolis, Minnesota and a B.A. degree in Chemistry in 1986 from Oberlin College in Oberlin, Ohio. Since 2000, I have worked in various capacities as a research and development chemist in the pharmaceutical field. I have extensive experience in the chemistry aspects of the development of pharmaceutical drug substances and drug products.

2. Since 2011, I have been employed at Chyall Pharmaceutical Consulting, LLC, which is my independent consulting company. Prior to my current position, I was employed at Aptuit, Inc. (formerly SSCI, Inc.) in West Lafayette, Indiana in the following roles: Director (2010-2011), Principal (2007-2010), Senior Research Investigator (2003-2006), and Research Investigator (2000-2003). Prior to Aptuit, I was employed as a Research Chemist at Great Lakes Chemical (now Chemtura) in West Lafayette, Indiana, from 1996-2000.

3. As of August 30, 2011, which I understand is the earliest possible effective filing date for the subject patent application, I was actively engaged in scientific research in the development of pharmaceutical products, including lyophilized pharmaceutical products to which the subject patent application pertains. I am aware of the general knowledge available in the field of lyophilization and of the skill level of the ordinary artisan in the field of lyophilization as it exists today and as it existed as of August 30, 2011.

4. A copy of my curriculum vitae is attached as Exhibit A.

5. I am being compensated by Fresenius Kabi USA for my time spent preparing this declaration. I have no financial interest in Fresenius Kabi USA, nor in the outcome of this prosecution. I do not personally know the inventors listed on the subject patent application. I offer my opinions on this matter as an independent pharmaceutical consultant. In addition to the materials cited here, I have relied on my general knowledge and education in this subject matter along with my 14 years of experience in the pharmaceutical industry.

6. I have reviewed the subject patent application. I understand that the pending claims are directed to a lyophilized solid composition containing levothyroxine sodium, a phosphate buffer, and mannitol, wherein the levothyroxine sodium and mannitol are present in particular amounts and ratios with respect to one another.

7. I have reviewed the Office Action dated March 6, 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"). I have also

conducted a scientific literature review concerning the stability of sodium levothyroxine pharmaceutical compositions.

8. It is my understanding that the Examiner believes the teachings of Baheti and Kim suggest to one of ordinary skill in the art that increasing the ratio of mannitol to levothyroxine would lead to an increase in the crystallization of mannitol which, in turn, would destabilize levothyroxine (Office Action at pg. 12, para. 2 – pg. 13, para. 2 and pg. 15, para. 1-2). Therefore, the Examiner believes that it would have been obvious to one of ordinary skill in the art to reduce the amount of mannitol in a lyophilized solid in order to stabilize levothyroxine.

9. I respectfully disagree with the Examiner's views of the teachings of the cited references as a whole, and the general knowledge in the field of lyophilization at the time of the invention. Given below are my opinions concerning how a skilled artisan would view these teachings with respect to the claims of the subject patent application.

10. Baheti discloses: "Crystallization of the bulking agent, however, might adversely affect the physical stability of the product in certain instances, for which, an amorphous bulking agent would be preferred" (pg. 46, col. 2) (emphasis added). In support of this statement, Baheti references an article by Herman et al. (*Pharm. Res., 11*: 1467-1473 (1994) ("Herman")). The Herman article discloses that the rate of hydrolysis of methylprednisolone sodium succinate increased as the ratio of mannitol to drug increased from 1 to 1 to 5.25 to 1 in a freeze-dried composition (pg. 1468, col. 1, and Figure 1).

11. It is my understanding that the Examiner has correlated the Herman studies concerning the hydrolytic stability of lyophilized methylprednisolone sodium succinate compositions to the stability of sodium levothyroxine compositions. I do not believe that the findings of Herman are relevant to a lyophilized solid levothyroxine composition for several reasons. The reactivity of water toward a given organic molecule is related to both the identity and the specific reactivity of the functional groups within a given molecule.

The different functional groups of different molecules will necessarily involve different rates of reaction with water, presuming any reaction even occurs.

12. Methylprednisolone sodium succinate and levothyroxine are unrelated in chemical structure and will therefore have different hydrolytic stability profiles. Most importantly, the degradation pathways for methylprednisolone sodium succinate in the presence of water are not possible for sodium levothyroxine due to these differences in chemical structure. Methylprednisolone sodium succinate degrades primarily by ester hydrolysis (pg. 1468, col. 1). In contrast, levothyroxine degrades primarily by deiodination of levothyroxine to liothyronine (subject patent application at paragraph 0033, and Figs. 2 and 3). The mechanism of ester hydrolysis involves attack of the carbonyl group (C=O) of the ester followed by cleavage of the C-O bond between the acyl group and the oxygen atom.

13. The ester hydrolysis mechanism that is operative in the degradation of methylprednisolone sodium succinate is completely different than the proposed mechanisms of the deiodination of sodium levothyroxine in the presence of water, which involves cleavage of a carbon-iodine (C-I) bond. Won has studied the aqueous stability sodium levothyroxine under various conditions and has proposed at least two mechanisms for the deiodination of the molecule. Won, CM. "Kinetics of Degradation of Levothyroxine in Aqueous Solution and in Solid State," *Pharm. Res.*, 9: 131-137 (1992) ("Won"). The deiodination reaction was found to have a sigmoidal pH dependence (Fig. 3), which is different than that for the ester hydrolysis of methylprednisolone sodium succinate. The Won studies were conducted using an excess of water and, therefore, the effect of trace amounts of water in lyophilized sodium levothyroxine compositions cannot be extrapolated from Won.

14. The Examiner has pointed to the better stability of methylprednisolone sodium succinate observed by Herman in the formulations that contained a greater amount of the drug relative to mannitol. Figure 1 of Herman provides a graph of the stabilities of these compositions. Upon review of the data contained in Herman, it is my opinion that

compositions that contain relatively less mannitol are not necessarily more stable than the compositions that contain greater relative amounts of mannitol. Figure 1 shows the stability of methylprednisolone sodium succinate over time. Notably, the amount of degradation over time provides roughly parallel lines for both mannitol formulations (open and closed triangles in Figure 1 of Herman). The initial measurements of the free methylprednisolone degradation product show that the starting amount of the degradation product was much higher for the 40 mg drug sample (5.25:1 mannitol:drug) (closed triangle), which has offset all subsequent measurements by this amount. Therefore, it is my opinion that any differences in the stability of the methylprednisolone sodium succinate samples as a function of added mannitol are slight. Regardless of the effect of mannitol concentration on methylprednisolone sodium succinate, it is my opinion that whatever mechanism to account for the instability of the drug toward water cannot be operative for the degradation of sodium levothyroxine due to the differences in chemical structure for the two drugs.

15. I also do not believe the teachings of Kim are relevant to the understanding of the stability of sodium levothyroxine in the presence of mannitol in a lyophilized composition. Kim discloses: "The physical state of mannitol during and after freeze-drying is particularly important in protein formulations where mannitol is present as a lyoprotectant. Izutsu et al., using three different model proteins, demonstrated that recovery of activity is inversely related to the degree of crystallinity of mannitol" (pg. 931, col. 2) (emphasis added). The impact of mannitol crystallinity on the biological activity of a protein in a freeze-dried preparation has no relation to the impact of mannitol crystallinity on the stability of a low molecular weight organic molecule, such as levothyroxine.

16. Kim also discloses that the relative concentration threshold above which crystalline mannitol is observed in a freeze-dried composition comprising mannitol and a cosolute is 30% w/w (pg. 933, col. 2). The relative concentration of mannitol in the exemplary freeze-dried compositions of the invention containing 3 mg mannitol disclosed

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