PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Thomas B. Ottoboni et al.	Examiner:	Miriam A. Levin
Application No.:	15/083,071	Art Unit:	1613
Filed:	March 28, 2016	CONF. NO:	9469

FOR: **EMULSION FORMULATIONS OF APREPITANT**

DECLARATION UNDER 37 C.F.R. §1.132

Mail Stop: Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Madam:

I, Thomas Ottoboni, declare as follows:

1. I currently hold the position of Senior Vice President at Heron Therapeutics and have been employed by Heron Therapeutics (formerly A. P. Pharma) since 2012. In my position at Heron Therapeutics, I supervise a group of 10 scientists responsible for the development of new products. This encompasses formulation development, analytical chemistry, as well as all preclinical evaluations.

2. My academic credentials include a Ph.D. in organic chemistry (U.C. Berkeley), a master of science (M.S.) degree in organic chemistry (S.F. State University), and a bachelor of science (B.S.) degree (U. C. Berkeley).

3. I am an inventor or co-inventor on 21 issued U.S. patents and on 14 pending U.S. patent publications directed to a variety of technologies including contrast agents, microparticles, emulsions, drug delivery, pharmaceuticals, and polyorthoester-based delivery systems.

4. I am a co-author of seven technical publications in various peer-reviewed journals including *J Exp Pharmacology, Contrast Media Mol Imaging, Magn Reson Med.*, and *Tetrahedron Letters,* and have presented scientific talks at numerous scientific meetings

including the Annual Scientific Sessions of the American Heart Association, the Annual Scientific Sessions of the American Society of Echocardiography, and the Scientific Meeting of the International Society for Magnetic Resonance in Medicine.

5. My Curriculum Vitae is attached hereto as Exhibit A.

6. I am a named co-inventor in the instant patent application, U.S. Application No. 15/083,071. I am familiar with the contents of the pending application, and have read and understand the claims that are currently pending in the instant application. I have also reviewed and am familiar with both the Examiner's remarks in the non final Office action mailed June 3, 2016 (hereinafter "non final Office action") and the art cited therein. I was also present during the telephonic interview held with Examiner Levin held on August 25, 2016 and have read the Examiner's Interview Summary mailed August 31, 2016 (hereinafter "Examiner Interview Summary").

7. The Examiner has identified Zhou (Chinese patent application publication number CN 102379845, an English translation of which was submitted by Applicants in the IDS dated April 12, 2016) as the primary reference in a rejection under 35 U.S.C. § 103(a) in the non final Office action. Zhou describes oil-in-water emulsions of aprepitant and provides 8 examples describing preparation of aprepitant emulsions. Zhou teaches an aprepitant emulsion which comprises 0.5 to 2.0 wt%, preferably 1.0 to 1.5 wt% aprepitant, 5 to 30 wt%, preferably 7 to 15 wt% oil, wherein the oil is soybean oil, 0.5 to 10 wt%, preferably 8 to 10 wt% emulsifier, wherein the emulsifier is egg yolk phospholipids, 1 to 10 wt%, preferably 2 to 5 wt% co-emulsifier, wherein the co-emulsifier is ethanol, and 5 to 20 wt%, preferably 8 to 13 wt% protective agent, wherein the protective agent may be glycerin, sucrose or glucose. The pH of the emulsion is 6.0 to 8.0.

8. The Examiner stated in the non final Office action that the only ingredient recited in the instant claims with a range that does not at least touch the range taught by Zhou is that of the emulsifier. The Examiner further states that Zhou teaches 0.5 to 10 wt% emulsifier, preferably 8 to 10 wt% wherein the emulsifier is egg yolk phospholipids. The instant claims recite 13 to 15 wt% egg yolk lecithin.

9. During the telephonic interview, I explained that the instant claims were not obvious over Zhou for at least the reason that the claimed pharmaceutical emulsion possessed unexpected and unpredictable properties relative to Zhou. Specifically, as summarized in Table 7 of the

instant specification as filed, the pharmaceutical aprepitant emulsions prepared as described in Examples 1, 2, 3, and 6 were stable at room temperature for at least 2 months. In contrast, the aprepitant emulsions taught by Zhou were not stable. We discovered this problem with the emulsions of Zhou by preparing emulsions as taught by Zhou. Two emulsion formulations which comprise the ingredients taught by Zhou were prepared and are described in Examples 4 and 5 of the instant application. The Examples show that emulsions according to the teachings of Zhou are not stable and form crystals within 4 days of storage at room temperature.

10. The Examiner asked about possible differences between the preparation method described by Zhou, specifically Example 1 in Zhou, and the preparation method described in Example 4 of the instant application. The Examiner requested that I submit a declaration to provide clarity regarding the teachings of Zhou and to show that the methods of Zhou were the same as those used in Example 4 of the instant application in order to support the argument that the claimed range of 13 to 15 wt% egg yolk lecithin results in an unpredictable increase in stability of the claimed pharmaceutical aprepitant emulsion in view of Zhou.

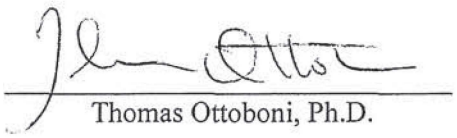
11. The Examiner noted that Zhou teaches that "soybean oil was added to the coarse emulsion and an appropriate amount of ethanol was added to dissolve the [sic] them." The Examiner noted during the telephonic interview that Example 4 of the instant specification does not teach adding soybean oil to the emulsion but then also noted in the Examiner Interview Summary dated August 31, 2016 that the preparation of Example 2 "does not have two phases at that point." I have carefully read Example 2 of Zhou and my understanding is that the phrase "soybean oil was added to the coarse emulsion" represents an inaccuracy in translation with respect to the use of the word "emulsion" because up to this point it is clear that no emulsion (mixture of an oil phase and an aqueous phase) exists. Instead, soybean oil is being added to a mixture of aprepitant, egg yolk phospholipid (the ethanol added with the aprepitant and egg yolk phospholipid had evaporated) to generate the oil phase. Accordingly, Example 4 of the instant application followed a procedure identical to Example 2 of Zhou in that aprepitant, egg yolk lecithin and ethanol were combined, dissolved by heating and stirring at 60°C until the ethanol was evaporated, and the soybean oil was then added to the mixture (described as a "thick residue" in Example 4 of the instant application and described as a "coarse emulsion" in the English translation of Zhou).

12. Another potential discrepancy questioned by the Examiner between Example 4 of the instant application and Example 1 of Zhou is that Zhou appears to dissolve the "sticky residue with soybean oil and ethanol before heating," but Example 4 of the instant application appears to require heating to dissolve the material. When I read Zhou Example 1, my understanding of the phrase "soybean oil was added to the coarse emulsion and an appropriate amount of ethanol was added to dissolve the them" describes the function of the soybean oil and ethanol, and that heating at 60°C was necessary to fully dissolve the oil and ethanol in the prepared mixture of aprepitant and egg yolk lecithin. Zhou did not intend to suggest or describe dissolution of the soybean oil and ethanol in the mixture of aprepitant and egg yolk lecithin prior to heating. Again, I believe that the aprepitant emulsion described in Example 4 was prepared in the same manner as the aprepitant emulsion prepared in Zhou.

13. Accordingly, based upon my knowledge and expertise in the area of organic chemistry and the preparation of pharmaceutical emulsions, it is my opinion that the methods taught by Zhou in at least Example 1 do not differ from the method taught in Example 4 of the instant specification.

14. I 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. I declare 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 instant application or any patent issuing thereon.

Aug 31 2016
Date



Thomas Ottoboni, Ph.D.