**WHAT IS CLAIMED IS:**

1. A physically stable pharmaceutical composition, comprising:
aprepitant;
an emulsifier;
an oil; and
water;
wherein the ratio of the emulsifier to aprepitant (wt%:wt%) ranges from about 18:1 to 22:1, wherein the ratio of the oil to aprepitant (wt%:wt%) ranges from about 11:1 to 15:1, and
wherein the composition is an emulsion.

2. The composition according to claim 1, wherein the composition comprises 0.4 wt/wt% to 1.0 wt/wt% aprepitant.

3. The composition according to claim 1, wherein the composition comprises 0.7 wt/wt% aprepitant.

4. The composition according to claim 1, wherein the composition comprises 11 wt/wt% to 15 wt/wt% emulsifier.

5. The composition according to claim 1, wherein the composition comprises 14 wt/wt% emulsifier.

6. The composition according to claim 1, wherein the emulsifier is egg yolk lecithin.

7. The composition according to claim 1, wherein the composition comprises 9 wt/wt% to 10 wt/wt% oil.

8. The composition according to claim 1, wherein the oil is soybean oil.



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9. The composition according to claim 1, wherein the composition further comprises sodium oleate as a pH modifier.

10. The composition according to claim 1, wherein the pH of the composition ranges from 7.5 to 9.0.

11. The composition according to claim 1, wherein composition further comprises 3 wt/wt% to 8 wt/wt% sucrose.

12. The composition according to claim 1, wherein the composition further comprises 5 wt/wt% sucrose.

13. The composition according to claim 1, wherein the composition further comprises 2 wt/wt% to 6 wt/wt% ethanol.

14. The composition according to claim 1, wherein the composition further comprises less than 6 wt/wt% ethanol.

15. A physically stable pharmaceutical composition, comprising:
aprepitant;
egg yolk lecithin;
soybean oil; and
water;
wherein the ratio of the egg yolk lecithin to aprepitant (wt%:wt%) is 20:1,
wherein the ratio of soybean oil to aprepitant (wt%:wt%) is 13:1,
wherein the composition is an emulsion.

16. The composition according to claim 15, wherein the composition comprises 0.7 wt/wt% aprepitant.

17. The composition according to claim 15, wherein the composition comprises 9 wt/wt% to 10 wt/wt% soybean oil.

18. The composition according to claim 15, wherein the composition further comprises sodium oleate as a pH modifier.

19. The composition according to claim 15, wherein the pH of the composition ranges from 7.5 to 9.0.

20. The composition according to claim 15, wherein the composition further comprises 5 wt/wt% sucrose.

21. The composition according to claim 15, wherein the composition further comprises 2 wt/wt% to 6 wt/wt% ethanol.

22. The composition according to claim 15, wherein the composition further comprises less than 4 wt/wt% ethanol.

# Electronic Acknowledgement Receipt

| | |
|---|---|
| **EFS ID:** | 30372144 |
| **Application Number:** | 15705201 |
| **International Application Number:** | |
| **Confirmation Number:** | 1822 |
| **Title of Invention:** | EMULSION FORMULATIONS OF APREPITANT |
| **First Named Inventor/Applicant Name:** | Thomas B. Ottoboni |
| **Customer Number:** | 108547 |
| **Filer:** | Wen Li/Julie Costello |
| **Filer Authorized By:** | Wen Li |
| **Attorney Docket Number:** | 092459-0218/8027.US03 |
| **Receipt Date:** | 14-SEP-2017 |
| **Filing Date:** | |
| **Time Stamp:** | 21:13:58 |
| **Application Type:** | Utility under 35 USC 111(a) |

## Payment information:

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| Submitted with Payment | yes |
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| Deposit Account | 505907 |
| Authorized User | Julie Costello |

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37 CFR 1.17 (Patent application and reexamination processing fees)

37 CFR 1.21 (Miscellaneous fees and charges)

## File Listing:

| Document Number | Document Description | File Name | File Size(Bytes)/ Message Digest | Multi Part /.zip | Pages (if appl.) |
|---|---|---|---|---|---|
| 1 | TrackOne Request | 092459_0218_req_t1.pdf | 113943<br>9e80fca5cb3fb260810171447a5608e3c8f0ed56 | no | 2 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 2 | Application Data Sheet | 092459_0218_ads.pdf | 117222<br>418e253567003757105c8d46ba1479cd530fce8e | no | 7 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| This is not an USPTO supplied ADS fillable form | | | | | |
| 3 | Oath or Declaration filed | 092459_0218_decs.pdf | 163231<br>a6a84f8a41ec889105e365c38f2c4f98f418e347 | no | 2 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 4 | | 092459_0218_CON_appln.pdf | 223188<br>640bb9de40cb62beca87c57b433575eab2e5c27b | yes | 33 |

**Multipart Description/PDF files in .zip description**

| Document Description | Start | End |
|---|---|---|
| Specification | 1 | 30 |
| Claims | 31 | 32 |
| Abstract | 33 | 33 |

**Warnings:**

**Information:**

| | | | | | |
|---|---|---|---|---|---|
| 5 | Drawings-only black and white line drawings | 092459_0218_figs.pdf | 322876<br>047007522a6a0045dbbaa1e576518dabc38b6046 | no | 4 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 6 | Fee Worksheet (SB06) | fee-info.pdf | 41848<br>9e6ab53771c5fd7bf780e8d39c09e578222585f1 | no | 2 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
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**New Applications Under 35 U.S.C. 111**
**If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.**
**National Stage of an International Application under 35 U.S.C. 371**
**If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.**
**New International Application Filed with the USPTO as a Receiving Office**
**If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.**

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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 15/705,201 | 09/14/2017 | Thomas B. Ottoboni | 092459-0218/8027.US03 | 1822 |

108547 7590 10/19/2017
McDermott Will & Emery LLP
500 North Capitol Street NW
Washington, DC 20001

| EXAMINER |
|---|
| LEVIN, MIRIAM A |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1613 | |

| NOTIFICATION DATE | DELIVERY MODE |
|---|---|
| 10/19/2017 | ELECTRONIC |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mweipdocket@mwe.com

| Office Action Summary | Application No. 15/705,201 | Applicant(s) Ottoboni et al. | |
|---|---|---|---|
| | Examiner MIRIAM A LEVIN | Art Unit 1613 | AIA Status Yes |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☑ Responsive to communication(s) filed on 14 September 2017 .

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____ .

2a)☐ This action is **FINAL.** 2b) ☑ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims***

5)☑ Claim(s) 1-22 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☑ Claim(s) 1-22 is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

**Application Papers**

10)☐ The specification is objected to by the Examiner.

11)☑ The drawing(s) filed on 14 September 2017 is/are: a)☑ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

**Certified copies:**

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☑ Notice of References Cited (PTO-892)

2) ☐ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____ .

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____ .

4) ☐ Other: _____ .

*Notice of Pre-AIA or AIA Status*

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

**DETAILED ACTION**

**Status of Claims**

1. Claims Pending: 1 - 22
2. New claims: 1 - 22
3. Amended claims: None
4. Canceled Claims: None
5. Change in Dependency: None

6. Objections/Rejections withdrawn: N/A

7. Rejections maintained with revision: N/A

8. New Grounds and/or Rejections necessitated by amendment:
   a. 35 USC 103 over Zhou vs. cl. 1 – 22
   b. Double patenting vs:
      i. US 9,561,229 B2
      ii. 14/859,013
      iii. 15/012,532
      iv. 15/398,928
      v. 15/705,208

9. Terminal Disclaimers:None

10. The following rejections constitute the complete set of rejections currently applied against the instant claims.

*Claim Rejections - 35 USC § 103*

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary

skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

3. Claims 1 – 8, 10 – 17 and 19 - 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhou et al. (CN 102379845 A; Pub. March 21, 2012 (17 pages including translation), page number used in citations below is the page number at the bottom of the respective page of the translation), as evidenced by Hawley (Glycerol, Hawley's Condensed Chemical Dictionary (published online 2007) [Retrieved from internet <URL: http://onlinelibrary.wiley.com/doi/10.1002/9780470114735.hawley07894/full >], 8 pages including bibliographic data) and Merck Index (Glycerol, The Merck Index Online (last revised 2013), [Retrieved from internet <URL: https://www.rsc.org/Merck-Index/monograph/print/m5790/glycerol?q=authorize >], 2 pages).

4. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Applicant claims:

6. A physically stable pharmaceutical composition, comprising: aprepitant;

7. an emulsifier; an oil; and water;

8. wherein the ratio of the emulsifier to aprepitant (wt%:wt%) ranges from about 18:1 to 22:1, wherein the ratio of the oil to aprepitant (wt%:wt%) ranges from about 11:1 to 15:1, and

9. wherein the composition is an emulsion.

**Determination of the scope and content of the prior art (MPEP 2141.01)**

10. Zhou teaches (claim 1 was reformatted by the Examiner to make it easier to read and compare to the instant claims):

> 1. An aprepitant microemulsion for injection, characterized in that it is consisting of the following components in percentages by mass:
> 0.05 % - 2% of aprepitant,
> 5% - 30% of oil for injection,
> 0.5% - 10% of emulsifier,
> 1% - 10% of co-emulsifier,
> 5% - 20% of protective agent, and
> 60% - 80% of water for injection;
>
> the oil for injection is one or several of soybean oil, ethyl oleate, polyethylene glycol glyceryl oleate, triglycerides of medium fatty chain length, isopropyl myristate, peanut oil, com oil, olive oil for injection;
>
> the emulsifier is one or several of phospholipids, poloxamer, polyoxyethylene castor oil and derivatives, polyethylene glycol - caprylic *I* capric acid glycerides, polysorbate 80;
>
> the co-emulsifier is one or several of ethanol, glycerol, 1,2-propylene glycol, polyethylene glycol 400;
>
> and the protective agent is one or several of glycerin, sucrose, trehalose, glucose, xylitol, mannitol, amino acids.
>
> 5. The aprepitant microemulsion for injection according to claim 1, characterized in that the oil for injection is soybean oil for injection.
>
> 6. The aprepitant microemulsion for injection according to claim 1, characterized in that the emulsifier is egg yolk phospholipid.
>
> 7. The aprepitant microemulsion for injection according to claim l, characterized in

that the co-emulsifier is ethanol.

8. The aprepitant microemulsion for injection according to claim 1, characterized in that the protective agent is glycerin.

9. The aprepitant microemulsion for injection according to claim 1, characterized in that it is consisting of the following components in percentages by mass: 1.0% - 1.5 % of aprepitant, 7% - 15% of oil for injection, 8% - 10% of emulsifier, 2% - 5% of co-emulsifier, 8% - 13% of protective agent, and 60% - 69% of water for injection.

11. Zhou teaches a pH of 6.0 – 8.0. (cl. 10)

12. Hawley's evidences that glycerol is an emulsifying agent. (p. 8)

13. Merck Index evidences that glycerin is glycerol. (p. 1, additional names)

**Ascertainment of the difference between the prior art and the claims (MPEP 2141.02)**

14. The difference between the instant application and Zhou is that Zhou does not expressly teach ranges that are identical to those instantly claimed, but instead teaches ranges which render the instantly claimed ranges obvious.

15. The difference between the instant application and Zhou is that Zhou does not expressly teach the same roles / intended uses for some of the claimed ingredients.

**Finding of prima facie obviousness**
**Rationale and Motivation (MPEP 2142-2143)**

16. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to prepare a composition comprising the instantly claimed ingredients, within the ranges instantly claimed, as suggested by Zhou, and produce the instant invention.

17. One of ordinary skill in the art would have been motivated to do this because Zhou teaches ingredients and ranges which would produce the instantly claimed composition.

18. In regard to the **ratio of emulsifier to aprepitant**, Zhou teaches 0.05 wt. % - 2.0 wt. % aprepitant, 0.5 – 10 wt. % emulsifier (cl. 1). This gives a range of 0.5 / 2.0 to 10 / 0.05 or **0.25:1 to 20:1**, which overlaps the instantly claimed range.

19. Moreover, Zhou teaches glycerol as a co-emulsifier and glycerin as a protective agent. As discussed above, **Merck** evidences that glycerin is glycerol and **Hawley** evidences that glycerol is an emulsifier. Zhou teaches 1 – 10 wt. % co-emulsifier and 5 – 20 wt. % protective agent. If both of these are glycerol (glycerin), then the amount of emulsifier actually ranges from 6.5 wt. % - 40 wt. %.

20. This would give a range of ratios of 6.5 / 2.0 to 40 / 0.05, which is **3.25:1 to 800:1**. More conservatively, if the highest amount of emulsifier is used with the highest amount of aprepitant, and vice versa, a more conservative range would be 6.5 / 0.05 to 40 / 2, which is **130:1 to 20:1**.

21. Zhou recites a composition with 1 – 1.5 wt. % aprepitant, 8 – 10 wt. % emulsifier, 2 – 5 wt. % co-emulsifier and 8 – 13 wt. % protective agent. (cl. 9) If glycerol is used for co-emulsifier and protective agent, this gives a range of 28 / 1 to 18 / 1.5 or **28:1 to 12:1.**

22. In regard to the **ratio of oil to aprepitant**: Zhou teaches 0.05 – 2 wt. % aprepitant and 5 – 30 wt. % oil (cl. 1), which provides a range of 5 / 2 to 30 / 0.05 or **2.5:1 to 600:1**. Zhou further teaches 1 – 1.5 wt. % aprepitant and 7 – 15 wt. % oil, which gives a range of 7/1.5 to 15/1 or **4.67:1 to 15:1**.

23. In regard to ranges in general, the instantly claimed range falls within this range and is therefore obvious, in the absence of a demonstration of unexpected results or criticality of the range.

24. In the case where the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a *prima facie* case of obviousness exists. *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976). MPEP 2144.05 (I).

25. Claims 1 – 3 are rejected.

26. In regard to the **wt. % of emulsifier**, as discussed in regard to claim 1 above, glycerin is glycerol (Merck) and glycerol is an emulsifier (Hawley), therefore if glycerol is used as co-

emulsifier and/or protective agent, the amount of emulsifier can be as high as 40 wt. %. The instantly claimed range falls within this range and is therefore obvious (MPEP 2144.05 (I)), in the absence of a demonstration of unexpected results or criticality of the range.

27. Claims 4 and 5 are rejected.

28. Zhou teaches egg yolk phospholipid as the emulsifier. (cl. 6)

29. Instant claim 6 is rejected.

30. In regard to the range of 9 – 10 wt. % oil, Zhou teaches a composition with 7 – 15 wt. % oil. (cl. 9) The range is obvious over the range of Zhou. (MPEP 2144.05 (I)).

31. Claim 7 is rejected.

32. Zhou teaches soybean oil as a preferred oil. (cl. 5)

33. Claim 8 is rejected.

34. In regard to the pH of 7. 5to 9, Zhou teaches a pH of 6.0 – 8.0 (cl. 10). The ranges overlap and therefore the instantly claimed range is obvious. (MPEP 2144.05 (I))

35. Claim 10 is rejected.

36. In regard to sucrose, Zhou teach this as a protective agent, present at 5 – 20 wt. %, preferably 8 – 13 wt. %. (cl. 1, 9) These ranges overlap those instantly claimed and render them obvious. (MPEP 2144.05 (I))

37. Claims 11 and 12 are rejected.

38. In regard to the ethanol, Zhou teaches this as a co-emulsifier, present at 1 – 10 wt. %, preferably 2 – 5 wt. %. (cl. 1, 7, 9) These ranges overlap those instantly claimed and render them obvious. (MPEP 2144.05 (I))

39. Claims 13 and 14 are rejected.

40. In regard to claims 15 – 17 and 19 – 22, all of these limitations are addressed above. Claims 15 – 17 and 19 -22 are rejected.

41. A reference is analyzed using its broadest teachings. MPEP 2123 [R-5].

42. Where, as here, the specific combination of features claimed is disclosed within the broad teachings of the reference but the reference does not disclose the specific combination of variables, in a specific embodiment or in a working example, "picking and choosing" within several variables does not necessarily give rise to anticipation. Corning Glass Works v. Sumitomo Elec., 868 F.2d 1251, 1262 (Fed. Circ. 1989).

43. However, "when a patent simply arranges old elements with each performing the same function it had been known to perform and yields no more than one would expect from such an arrangement, the combination is obvious". KSR v. Teleflex, 127 S.Ct. 1727, 1740 (2007)(quoting Sakraida v. A.G. Pro, 425 U.S. 273, 282 (1976). "[W]hen the question is whether a patent claiming the combination of elements of prior art is obvious", the relevant question is "whether the improvement is more than the predictable use of prior art elements according to their established functions." (Id.). Addressing the issue of obviousness, the Supreme Court noted that the analysis under 35 USC 103 "need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." KSR v. Teleflex, 127 S.Ct. 1727, 1741 (2007). The Court emphasized that "[a] person of ordinary skill is ... a person of ordinary creativity, not an automaton." Id. at 1742.

44. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to rearrange the disclosed elements and embodiments of Zhou to prepare the claimed composition. Such a rearrangement by a person of ordinary skill in the art who is not an

automaton to yield the claimed composition is within the purview of the ordinary skilled artisan upon reading Zhou and would yield predictable results.

45. Claims 1 – 8, 10 – 17 and 19 – 22 are rejected.

46. In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a).

47. From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

48. Claims 9 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhou (CN 102379845 A; Pub. March 21, 2012 (17 pages including translation), page number used in citations below is the page number at the bottom of the respective page of the translation) (cited above), as evidenced by Hawley (Glycerol, Hawley's Condensed Chemical Dictionary (published online 2007) [Retrieved from internet <URL: http://onlinelibrary.wiley.com/doi/10.1002/9780470114735.hawley07894/full >], 8 pages including bibliographic data) (cited above) and Merck Index (Glycerol, The Merck Index Online (last revised 2013), [Retrieved from internet <URL: https://www.rsc.org/Merck-Index/monograph/print/m5790/glycerol?q=authorize >], 2 pages) (cited above), as applied to the claims above, and in further view of Cohen et al. (US 2003 / 0190323 A1).

**Determination of the scope and content of the prior art**
**(MPEP 2141.01)**

49. The teachings of Zhou are discussed above.

50. Zhou teaches adjusting the pH to 6.0 – 8.0 (cl. 10), but does not teach what compound(s) are used to adjust the pH.

**Ascertainment of the difference between the prior art and the claims (MPEP 2141.02)**

51. The difference between the instant application and Zhou is that Zhou teaches adjusting the pH to 6.0 – 8.0, but does not teach sodium oleate as the pH adjuster. This deficiency in Zhou is cured by the teachings of Cohen et al.

52. Cohen et al. teach preparations and methods for the treatment of T cell mediated diseases. (title; entire document) Cohen et al. teach a composition that is used for injection. (e.g., [0097], [0099], [0111]) Cohen et al. teach a composition comprising egg phospholipids, with sodium oleate as a pH adjuster. (e.g., [0119], [0120])

**Finding of prima facie obviousness Rationale and Motivation (MPEP 2142-2143)**

53. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to use sodium oleate to adjust the pH of the composition, as suggested by Zhou and Cohen et al., and produce the instant invention.

54. One of ordinary skill in the art would have been motivated to do this because sodium oleate is a material suitable for the intended use. Zhou teaches an injectable composition comprising egg phospholipids and teaches that the pH is adjusted, but does not teach what compounds are used to adjust the pH, and Cohen teaches an injectable composition comprising egg phospholipids wherein the pH is adjusted using sodium oleate. Zhou does not teach specific compounds to adjust the pH therefore, in the absence of evidence to the contrary or a demonstration of criticality or other unexpected results, any suitable compounds may be used.

Cohen demonstrates that sodium oleate is suitable for injectable compositions and for compositions comprising egg phospholipids.

11. Generally, it is *prima facie* obvious to select a known material for incorporation into a composition, based on its recognized suitability for its intended use. MPEP § 2144.07.

55. Claims 9 and 18 are rejected.

56. All of the claims have been rejected.

57. In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a).

58. From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van*

*Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting provided the reference application or patent either is shown to be commonly owned with the examined application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP §§ 706.02(l)(1) - 706.02(l)(3) for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

Claims 1 – 22 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1 – 21 of U.S. Patent No. 9,561,229 B2. Although the claims at issue are not identical, they are not patentably distinct from each other because both recite an injectable composition comprising the same compounds in the same weight percentages, or in overlapping ranges. (MPEP 2144.05 (I)) Where the instant claims are more generic: A genus is

anticipated by a species from that genus. (MPEP 2131.02 (I)) A composition is also obvious over a method of making it or using it.

Claims 1 – 22 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 18, 20 – 22 and 24 - 34 of copending Application No. 14/859,013 (reference application). Although the claims at issue are not identical, they are not patentably distinct from each other because both recite an injectable composition comprising the same compounds in the same weight percentages, or in overlapping ranges. (MPEP 2144.05 (I)) Where the instant claims are more generic: A genus is anticipated by a species from that genus. (MPEP 2131.02 (I)) A composition is also obvious over a method of making it or using it.

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

Claims 1 – 22 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1 – 3, 6 - 28 of copending Application No. 15/012,532 (reference application). Although the claims at issue are not identical, they are not patentably distinct from each other because both recite an injectable composition comprising the same compounds in the same weight percentages, or in overlapping ranges. (MPEP 2144.05 (I)) Where the instant claims are more generic: A genus is anticipated by a species from that genus. (MPEP 2131.02 (I)) A composition is also obvious over a method of making it or using it.

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

Claims 1 – 22 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1 - 17 of copending Application No. 15/398,928 (reference application). Although the claims at issue are not identical, they are not patentably distinct from each other because both recite an injectable composition comprising the same compounds in the same weight percentages, or in overlapping ranges. (MPEP 2144.05 (I)) Where the instant claims are more generic: A genus is anticipated by a species from that genus. (MPEP 2131.02 (I)) A composition is also obvious over a method of making it or using it.

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

Claims 1 – 22 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1 - 21 of copending Application No. 15/705,208 (reference application). Although the claims at issue are not identical, they are not patentably distinct from each other because both recite an injectable composition comprising the same compounds in the same weight percentages, or in overlapping ranges. (MPEP 2144.05 (I)) Where the instant claims are more generic: A genus is anticipated by a species from that genus. (MPEP 2131.02 (I)) A composition is also obvious over a method of making it or using it.

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

***Conclusion***

Claims 1 - 22 are rejected. No claims are allowed.

Any inquiry regarding this communication or earlier communications from the examiner should be directed to Miriam Levin whose telephone number is 571-270-3471. The examiner can normally be reached between the hours of 10:00 AM - 6:30 PM, EST, Monday - Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brian-Yong Kwon can be reached at 571-272-0581. The fax number for the organization where this application or proceeding is assigned is 571-273-4371.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, Applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

/M. A. L./

Examiner, Art Unit 1613

/ERNST V ARNOLD/
Primary Examiner, Art Unit 1613

**PATENT**

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | | | |
|---|---|---|---|
| In re Application of: | Thomas B. Ottoboni et al. | Examiner: | Miriam A. Levin |
| Application No.: | 15/705,201 | Art Unit: | 1613 |
| Filed: | September 14, 2017 | Conf. No: | 1822 |
| For: | **EMULSION FORMULATIONS OF APREPITANT** | | |

**AMENDMENT AND RESPONSE UNDER 37 C.F.R. § 1.111**

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

Commissioner:

The present communication responds to the non-final Office action dated October 19, 2017 in the above-referenced patent application.

**A Listing of the Claims** begins on page 2.

**Remarks** begin on page 5.

## CLAIMS

No claim amendment is made herein, and the listing of claims is provided below simply for convenience.

1. (Original) A physically stable pharmaceutical composition, comprising:

aprepitant;

an emulsifier;

an oil; and

water;

wherein the ratio of the emulsifier to aprepitant (wt%:wt%) ranges from about 18:1 to 22:1, wherein the ratio of the oil to aprepitant (wt%:wt%) ranges from about 11:1 to 15:1, and

wherein the composition is an emulsion.

2. (Original) The composition according to claim 1, wherein the composition comprises 0.4 wt/wt% to 1.0 wt/wt% aprepitant.

3. (Original) The composition according to claim 1, wherein the composition comprises 0.7 wt/wt% aprepitant.

4. (Original) The composition according to claim 1, wherein the composition comprises 11 wt/wt% to 15 wt/wt% emulsifier.

5. (Original) The composition according to claim 1, wherein the composition comprises 14 wt/wt% emulsifier.

6. (Original) The composition according to claim 1, wherein the emulsifier is egg yolk lecithin.

7. (Original) The composition according to claim 1, wherein the composition comprises 9 wt/wt% to 10 wt/wt% oil.

8. (Original) The composition according to claim 1, wherein the oil is soybean oil.

9. (Original) The composition according to claim 1, wherein the composition further comprises sodium oleate as a pH modifier.

10. (Original) The composition according to claim 1, wherein the pH of the composition ranges from 7.5 to 9.0.

11. (Original) The composition according to claim 1, wherein composition further comprises 3 wt/wt% to 8 wt/wt% sucrose.

12. (Original) The composition according to claim 1, wherein the composition further comprises 5 wt/wt% sucrose.

13. (Original) The composition according to claim 1, wherein the composition further comprises 2 wt/wt% to 6 wt/wt% ethanol.

14. (Original) The composition according to claim 1, wherein the composition further comprises less than 6 wt/wt% ethanol.

15. (Original) A physically stable pharmaceutical composition, comprising:

aprepitant;

egg yolk lecithin;

soybean oil; and

water;

wherein the ratio of the egg yolk lecithin to aprepitant (wt%:wt%) is 20:1,

wherein the ratio of soybean oil to aprepitant (wt%:wt%) is 13:1,

wherein the composition is an emulsion.

16. (Original) The composition according to claim 15, wherein the composition comprises 0.7 wt/wt% aprepitant.

17. (Original) The composition according to claim 15, wherein the composition comprises 9 wt/wt% to 10 wt/wt% soybean oil.

18. (Original) The composition according to claim 15, wherein the composition further comprises sodium oleate as a pH modifier.

19. (Original) The composition according to claim 15, wherein the pH of the composition ranges from 7.5 to 9.0.

20. (Original) The composition according to claim 15, wherein the composition further comprises 5 wt/wt% sucrose.

21. (Original) The composition according to claim 15, wherein the composition further comprises 2 wt/wt% to 6 wt/wt% ethanol.

22. (Original) The composition according to claim 15, wherein the composition further comprises less than 4 wt/wt% ethanol.

## REMARKS

Consideration of the remarks presented herein is respectfully requested.

### I. Status of the Claims

No claims are amended herein. Therefore, there is no issue of new matter.

Upon entry of this paper, claims 1-22 are pending and under examination.

### II. Claim Rejections -35 U.S.C. § 103(a)

Claims 1-8, 10-17, and 19-22 are rejected under 35 U.S.C. § 103(a) for allegedly being unpatentable over CN102379845A ("Zhou") as evidenced by Glycerol, Hawley's Condensed Chemical Dictionary (published online 2007) ("Hawley") and Glycerol, The Merck Index Online (last revised 2013) ("Merck Index"). Office Action at pp.3-9.

Claims 9 and 18 are rejected under 35 U.S.C. § 103(a) for allegedly being unpatentable over Zhou, as evidenced by Hawley and Merck Index, as applied to the claims above, and in further view of US 2003/0190323 ("Cohen"). *Id.* at pp. 9-11.

Specifically, admitting that Zhou is silent on the ratios of emulsifier to aprepitant and oil to aprepitant, the Office infers from Zhou the range of the ratio for emulsifier to aprepitant to be either 0.25:1 to 200:1[1], 3.25:1 to 800:1, 130:1 to 20:1, or 28:1 to 12:1, based on various disclosures of the respective weight percentages of emulsifier, co-emulsifier, and aprepitant. *Id.* at pp. 5-6, paragraphs 18-21. The Office makes similar inferences of the oil to aprepitant ratio to be either 2.5:1 to 600:1 or 4.67 to 15:1 based on Zhou's disclosures of individual weight percentages of aprepitant and oil. *Id.* at p.6, paragraph 22. The Office then argues that a prima facie case of obviousness exists because the claimed ranges for the ratios of emulsifier to aprepitant and oil to aprepitant overlap or lie inside the ranges inferred from Zhou. *Id.*, paragraph 24.

The rejections are traversed for the following reasons.

[1] The Office's indication of 0.25:1 to 20:1 at paragraph 18 of the Office Action is incorrect. Based on the formulae 0.5/2.0 to 10/0.05, the ratio should be 0.25:1 to 200:1.

The M.P.E.P. clearly provides that a prior art disclosing a range encompassing narrower claimed range is NOT always sufficient to establish a prima facie case of obviousness. In particular, M.P.E.P. § 2144.05 states that "if the reference's disclosed range is so broad as to encompass a very large number of possible distinct compositions, this might present a situation analogous to the obviousness of a species when the prior art broadly discloses a genus. *Id.* See also *In re Baird,* 16 F.3d 380, 29 USPQ2d 1550 (Fed. Cir. 1994); *In re Jones,* 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992); MPEP § 2144.08." And M.P.E.P. § 2144.08 (I) states "[t]he fact that a claimed species or subgenus is encompassed by a prior art genus is not sufficient by itself to establish a *prima facie* case of obviousness. *In re Baird,* 16 F.3d 380, 382, 29 USPQ2d 1550, 1552 (Fed. Cir. 1994)"

Here, assuming *arguendo* that it is reasonable for the Office to make inferences that Zhou teaches the ratios of emulsifier to aprepitant and oil to aprepitant based on Zhou's various disclosures of respective weight percentages of emulsifier (co-emulsifier), oil, and aprepitant, the facts i)- iii) below support a conclusion of non-obviousness in view of the law discussed above:

i) the Office inferred from Zhou four different ranges of the ratio for emulsifier to aprepitant: 0.25:1 to 200:1, 3.25:1 to 800:1, and 130:1 to 20:1, and 28:1 to 12:1,

ii) each of the inferred ratios is so broad as to encompass a very large number of possible distinct ratios, and

iii) the Office provides no other rationale as to why a skilled artisan would modify the inferred range so as to arrive at the claims reciting, among other things, a much narrower range of 18:1 to 22:1.

Moreover, "a patentable invention may lie in the discovery of the source of a problem even though the remedy may be obvious once the source of the problem is identified. This is part of the 'subject matter as a whole' which should always be considered in determining the obviousness of an invention under 35 U.S.C. § 103." M.P.E.P. § 2141.02 (III). Applicant asserts that the instant claims originate from the identification of a problem not previously recognized by Zhou.

Specifically, Applicant identified that the emulsifier to drug ratio may contribute significantly to the physical stability of aprepitant emulsions. Nowhere does Zhou recognize the formation of crystals, hence the issue of physical stability, in the emulsions produced. As shown

in Table 7 on pages 27 of the instant specification as filed, the formulations of Examples 1, 2, 3 and 6 were physically stable as demonstrated by the lack of crystal formation when the emulsions were stored at room temperature for at least 2 months in the case of Examples 1, 3 and 6, and for at least 3 months for Example 2. The pharmaceutical emulsions described in Examples 1, 2, 3, and 6 each fall within the scope of instant claim 1.

In contrast, as shown in Example 4 of the instant specification as filed, an emulsion of aprepitant comprising 9.95 wt/wt% emulsifier (Lipoid E 80) and 0.672 wt/wt% aprepitant, with the emulsifier to aprepitant ratio as 14.8:1, had crystals observed within 4 days post preparation at room temperature. Example 5 of the instant application as filed shows that an emulsion of aprepitant comprising 2.50 wt/wt% emulsifier (Lipoid E 80) and 0.250 wt/wt% aprepitant, with the emulsifier to aprepitant ratio as 10:1, also had crystals observed within 4 days post preparation at room temperature. Both emulsions described in Examples 4 and 5 fall outside the scope of current claims due to the ratio of emulsifier to aprepitant.

Also under M.P.E.P. § 2144.05 (III)(A), a *prima facie* case of obviousness can be rebutted by showing the criticality of the change. Indeed, the above evidence showing that the pharmaceutical emulsions are stable when the ratio for emulsifier to aprepitant is within the claimed range but not so when the ratio is outside the claimed range also demonstrates the criticality of the claimed range for the ratio of emulsifier to aprepitant.

For the foregoing reasons, the rejections should be withdrawn.

## III. Double Patenting

The Office rejects claims 1-22 on the ground of non-statutory double patenting as allegedly being unpatentable over claims 1-21of U.S. Patent No. **9,561,229**. *Id.* at pp. 12-13.

The Office provisionally rejects claims 1-22 on the ground of non-statutory double patenting as allegedly being unpatentable over 1) claims 18, 20-22, and 24-34 of U.S. Application No. 14/859,013 (now issued as U.S. Patent No. **9,808,465**), 2) claims 1-3 and 6-28 of U.S. Application No. **15/012,532**, 3) claims 1-17 of U.S. Application No. **15/398,928**, and 4) claims 1-21 of U.S. Application No. **15/705,208**. *Id.* at pp. 13-14.

Solely to expedite prosecution, Applicant hereby submits terminal disclaimers over the referenced patents/applications listed above to obviate the double patenting rejections.

## IV. Conclusion

Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 50-5907 and please credit any excess fees to such deposit account. If the Examiner has any questions or believes a telephone conference would expedite prosecution of this application, the Examiner is encouraged to call the undersigned at (650) 815-7399.

Respectfully submitted,
MCDERMOTT WILL & EMERY LLP

Date: January 19, 2018

/Wen Li/
Wen Li
Reg. No. 62,185

**Correspondence**
Customer No. 108547

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108547 7590 03/14/2018
McDermott Will & Emery LLP
500 North Capitol Street NW
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| EXAMINER |
|---|
| LEVIN, MIRIAM A |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1613 | |

DATE MAILED: 03/14/2018

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 15/705,201 | 09/14/2017 | Thomas B. Ottoboni | 092459-0218/8027.US03 | 1822 |

TITLE OF INVENTION: EMULSION FORMULATIONS OF APREPITANT

| APPLN. TYPE | ENTITY STATUS | ISSUE FEE DUE | PUBLICATION FEE DUE | PREV. PAID ISSUE FEE | TOTAL FEE(S) DUE | DATE DUE |
|---|---|---|---|---|---|---|
| REGULAR | SMALL | $500 | $0.00 | $0.00 | $500 | 06/14/2018 |

**THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.**

**THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.**

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(Depositor's name)
(Signature)
(Date)

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 15/705,201 | 09/14/2017 | Thomas B. Ottoboni | 092459-0218/8027.US03 | 1822 |

TITLE OF INVENTION: EMULSION FORMULATIONS OF APREPITANT

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| REGULAR | SMALL | $500 | $0.00 | $0.00 | $500 | 06/14/2018 |

| EXAMINER | ART UNIT | CLASS-SUBCLASS |
|---|---|---|
| LEVIN, MIRIAM A | 1613 | 424-400000 |

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2 _____
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3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

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❑ Advance Order - # of Copies _____

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❑ The director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

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❑ Applicant asserting small entity status. See 37 CFR 1.27

❑ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
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108547 7590 03/14/2018
McDermott Will & Emery LLP
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Washington, DISTRICT OF COLUMBIA 20001

| EXAMINER |
|---|
| LEVIN, MIRIAM A |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1613 | |

DATE MAILED: 03/14/2018

## OMB Clearance and PRA Burden Statement for PTOL-85 Part B

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The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

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**The Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

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1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
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5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

| Notice of Allowability | Application No. 15/705,201 | Applicant(s) Ottoboni et al. | |
|---|---|---|---|
| | Examiner MIRIAM A LEVIN | Art Unit 1613 | AIA Status Yes |

***-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--***

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☑ This communication is responsive to IDS, TD, Response to NonFinal Office Action filed Jan. 19, 2018.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☑ The allowed claim(s) is/are 1-22 . As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see **http://www.uspto.gov/patents/init_events/pph/index.jsp** or send an inquiry to **PPHfeedback@uspto.gov.**

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   **Certified copies:**

   a) ☐ All  b) ☐ Some  *c) ☐ None of the:

   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file areply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
**THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.**

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .

   **Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).**

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

**Attachment(s)**

1. ☑ Notice of References Cited (PTO-892)
2. ☑ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date. _____.
5. ☐ Examiner's Amendment/Comment
6. ☑ Examiner's Statement of Reasons for Allowance
7. ☑ Other See Continuation Sheet.

/ERNST V ARNOLD/
Primary Examiner, Art Unit 1613

Continuation of Attachment(s) 7. Other: Search notes, search history, index clasification, NPL literature, FOR reference

### *Notice of Pre-AIA or AIA Status*

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

## DETAILED ACTION

### Status of Claims

1. Claims Pending: 1 - 22
2. New claims: None
3. Amended claims: None
4. Canceled Claims: None
5. Change in Dependency: None

6. Objections/Rejections withdrawn:

    a. 35 USC 103 over Zhou vs. cl. 1 – 22
    b. Double patenting vs:
        i. US 9,561,229
        ii. US 9,808,465 (US application 14/859,013)
        iii. 15/012,532
        iv. 15/398,928
        v. 15/705,208

7. Rejections maintained with revision: None

8. New Grounds and/or Rejections necessitated by amendment: None

9. Terminal Disclaimers: filed and approved January 19, 2018
    vi. US 9,561,229 B2
    vii. US 9,808,465 (application 14/859,013)
    viii. 15/012,532
    ix. 15/398,928
    x. 15/705,208

10. Applicant's arguments filed January 19, 2018 have been fully considered. There are no rejections applied against the instant claims.

### *Allowable Subject Matter*

Claims 1- 22 are allowed.

The following is an examiner's statement of reasons for allowance:

As indicated in the Allowability Notice for parent application 14/859,013, Examiner Levin and Primary Examiner Ernst Arnold acknowledge that Applicant demonstrated unexpected results in regard to the physical stability of the instantly claimed composition and thereby overcame a rejection over Zhou et al., CN 102 379 845 A.

The physical stability is related to a demonstration of criticality of the claimed range for the ratio of emulsifier to aprepitant, at least when compared to lower ratios which are exemplified in some prior art references. (Note Remarks filed Jan. 19, 2018, pp. 6, 7. See also attached Interview Summary and Dec. of Thomas Ottoboni.)

Therefore, prior art references are overcome by one or more of the following: (1) unexpected results in regard to physical stability and/or (2) lack of motivation or insufficient motivation to prepare a composition comprising the requisite ratio of both emulsifier to aprepitant and oil to aprepitant. While these may not be all possible reasons for allowance, the Examiner finds them sufficient.

The closest prior art references are:

1. Zhou et al., CN 10 2379845 A (March 21, 2012) (cited on IDS, copy in parent; cited on Form 892, copy attached, including English language translation). Zhou et al. teaches a composition comprising:
    a. 0.05 – 2 wt. % aprepitant,
    b. 5 – 30 % oil for injection,
    c. 0.5 – 10 % emulsifier,
    d. 1- 10 % co-emulsifier,
    e. 5 – 20 wt. % protective agent, and

f. 60 – 80 wt. % water for injection. (Abs., cl. 1; see also examples)

g. Wherein the oil may be soybean oil (cl. 1, 5), the emulsifier may be egg yolk phospholipid (cl. 1, 6), the co-emulsifier may be ethanol (cl. 1, 7), the protective agent may be sucrose (cl. 1), and the pH is 6 – 8 (cl. 10).

2. Hignorani et al., US 2013 / 0317016 A1 (cited on IDS), (relevant dates: provisional application filed Mary 24, 2012; application filed May 24, 2013; publication Nov. 28, 2013). Hignorani et al. teaches exemplary emulsions comprising:

   a. about 0.1 wt. % aprepitant,

   b. about 9.2 wt. % soybean oil (13 mL, density 0.91 – 0.93 g/mL), and

   c. 1.2 wt. % Lipoid E80 ([0055], [0056] – Tables 11 and 12).

   d. Note:

      i. Lipoid E80 is the egg yolk lecithin used in the examples of the instant specification.

      ii. The ratio of egg yolk lecithin to aprepitant in the cited examples of Hignorani et al. is 12:1.

   e. Hignorani et al. teach egg yolk lecithin as a surfactant (e.g. [0023]) and teach using 0.1 – 1 w/v %, 1.0 – 3.0 w/v % or 3 – 5 w/v %, and "in some cases even higher" amounts of surfactant. (e.g. [0024])

   f. The formulations are physically stable, i.e. they do not precipitate out of solution "for extended periods of time." (e.g., [0052]) Extended periods of time appears to mean at least 24 hours (e.g. [0050])

g. While other distinctions may apply, at minimum Hignorani et al. do not teach or suggest using 13 – 15 wt. % emulsifier, or a ratio of 18:1 – 22:1 of egg yolk lecithin to aprepitant in a final formulation, and provide insufficient motivation to optimize the formulation to include that high a percentage of emulsifier / surfactant and/or that high a ratio of emulsifier to aprepitant in a composition that also contains oil.

h. It is noted that Hignorani et al. recognize that aprepitant is substantially insoluble in both water and oil. (e.g. [0054])

i. It is also noted that Hignorani et al. teach an example with 11 mg/mL Polysorbate 80 and 0.560 mg/mL aprepitant ([0047], Table 4). While this example has a ratio of about 19.6 to 1 for emulsifier to aprepitant, which falls within the range recited by instant claim 1, the composition does not contain any oil, which is required by instant claim 1.

3. Zhou et al., Preparation of Aprepitant Emulsion for Intravenous Injection, Chinese Journal of Pharmaceuticals (2012), 43(12): 1003 – 1006, English translation (cited on IDS; copy in parent; cited on Form 892, copy attached hereto). Zhou et al. teach optimizing an emulsion wherein the optimal formulation comprises:

a. 0.25 % aprepitant,

b. 15 % soybean oil,

c. 2.5 % egg yolk lecithin E80,

d. oleic acid 0.125 % (Abs.; p. 1004 – 1005, Sec. 2.3),

e. wherein water for injection is added in a 1.5:8.5 ratio (p. 1005, sec. 2.4).

4. A small amount of ethanol is added to solubilize the ingredients, and is then removed. (p. 1005, col. 1, Sec. 2.4)
5. The optimized formulation comprises a ratio of 10:1 for egg yolk lecithin to aprepitant. The optimized composition comprises no more than 2.5 % egg yolk lecithin; which is far less than the amount required by the instant claims.
6. In regard to stability of the emulsions, Zhou et al. teach:
   a. "Only the fat emulsion with 80 % lecithin is the most stable one. This kind of lecithin contains small amount of acidic lipids, can increase the surface charge of emulsion droplet, so as to be helpful to make the emulsion more stable . . ." (p. 1006, Discussion, Sec. 3.1, pr. 2. 80 % lecithin refers to "egg yolk lecithin E80" as evidenced by p. 1006, Discussion, Sec. 3.1, pr. 1)
   b. "But the oleic acid is able to work as a co-emulsifier. The addition of oleic acid can increase the stiffness of emulsion film, as well as increase the surface charge of emulsion, enhance the dispersion and reduce the aggregation function, easily obtain emulsion with smaller size of particle, enhance the stability of the emulsion. The dosage of oleic acid is 2.5 % to 5 % of the ones of phosphatide. . . " (p. 1006, col. 1 – 2, sec. 3.2)
7. Regardless, when Zhou et al. optimize their formulation, they try 2 % to 4 % of the egg yolk lecithin and teach that the best results are obtained with a

formulation using 2.5 %. (p. 1004, Sec. 2.3.1, Table 1) The optimized formulation of Zhou et al. comprises emulsifier in a 10:1 ratio vs. aprepitant, i.e., 0.25 % aprepitant and 2.5 % egg yolk lecithin. (e.g., Abs.) Therefore Zhou et al. provide insufficient motivation to increase the amount of egg yolk lecithin in the composition, or to provide a higher ratio of egg yolk lecithin / emulsifier to aprepitant.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

***Response to Arguments***

Applicant's arguments, see Remarks, filed January 19, 2018 have been fully considered and are persuasive.

In regard to the rejections over Zhou et al. under 35 USC 103, Applicant argues that unexpected results / criticality of the range is demonstrated by the examples and comparative examples in the instant specification. (Remarks, pp. 6, 7) As acknowledged above, the Examiner agrees.

The Examiner also notes Applicant's correction of the Examiner's calculation error in regard to the ratio of emulsifier to aprepitant found in Zhou. The ranges 0.05 – 2.0 % aprepitant and 0.5 – 10 % emulsifier produce a ratio of 0.25:1 to 200:1, NOT 0.25:1 to 20:1, as stated in the NonFinal Office Action. (This calculation of the range for

the ratio is based on 0.5 % emulsifier / 2 % aprepitant = 0.25:1, and 10 % emulsifier / 0.05 % aprepitant = 200:1.)

In regard to the double patenting rejections, a terminal disclaimer was filed and approved. (Remarks, pp. 7, 8) The rejections are withdrawn.

***Made of Record***

1. Declaration of Thomas Ottoboni under 37 C.F.R. § 1.132, filed September 1, 2016 in regard to U.S. Application 15/083,071, now US patent 9,561,229. The declaration provides information to clarify the testing procedures used in the comparative testing in the specification, examples 1 – 6, pp. 21 – 27. (See instant specification, Ex. 1 – 6, pp. 20 -16)

2. Applicant initiated interview, Examiner's Summary, August 31, 2016, for U.S. Application 15/083,071, now. U.S. Patent 9,561,229. The interview reflects discussion regarding the test data in Ex. 1 – 6 of the specification.

3. Lipoid GmbH, Lipoid Product Finder, [Retrieved from internet <URL: http://www.lipoid.com/en/node/105 >], (2018), 1 page. Evidences copyright date and evidences that Lipoid is derived from egg yolk lecithin and contains approx. 80 % phosphatidylcholine.

4. Lipoid GmbH, Lipoid Product Finder (print friendly version), [Retrieved from internet <URL: http://www.lipoid.com/en/print/105 >], (2018), 2 pages.

***Conclusion***

Claims 1 – 22 are allowed. No claims are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MIRIAM A LEVIN whose telephone number is (571)270-

3471. The examiner can normally be reached Monday – Friday between noon and 9 PM, Eastern Time.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brian-Yong S. Kwon can be reached on 571-272-0581. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/M.A.L/
Examiner, Art Unit 1613
/ERNST V ARNOLD/
Primary Examiner, Art Unit 1613