WHAT IS CLAIMED IS:

1. An injectable pharmaceutical emulsion comprising:

0.4 wt/wt% to 1.0 wt/wt% aprepitant;

13 wt/wt% to 15 wt/wt% egg yolk lecithin;

9 wt/wt% to 10 wt/wt% soybean oil; and

a pH modifier, wherein the pH modifier is sodium oleate;

wherein the pH of the emulsion ranges from 7.5 to 9.0.

2. The emulsion according to claim 1, wherein the emulsion comprises 0.7 wt/wt% aprepitant.

3. The emulsion according to claim 1, wherein the emulsion comprises 14 wt/wt% egg yolk lecithin.

4. The emulsion according to claim 1, wherein the emulsion further comprises 3 wt/wt% to 8 wt/wt% sucrose.

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

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

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

8. An injectable pharmaceutical emulsion comprising:

0.7 wt/wt% aprepitant;

14 wt/wt% egg yolk lecithin;

9 wt/wt% to 10 wt/wt% soybean oil; and

a pH modifier, wherein the pH modifier is sodium oleate;

wherein the pH of the emulsion ranges from 7.5 to 9.0.

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9. The emulsion according to claim 8, wherein the emulsion further comprises 5 wt/wt% sucrose.

10. The emulsion according to claim 8, wherein the emulsion further comprises 2 wt/wt% to 6 wt/wt% ethanol.

11. The emulsion according to claim 8, wherein the emulsion further comprises less than 4 wt/wt% ethanol.

12. A method for treating nausea and vomiting in a subject in need thereof comprising administering to the subject the pharmaceutical emulsion according to claim 1.

13. The method according to claim 12, wherein the nausea and vomiting is chemotherapy induced nausea and vomiting.

14. The method according to claim 13, wherein the chemotherapy induced nausea and vomiting is in response to highly emetic chemotherapy.

15. The method according to claim 13, wherein the chemotherapy induced nausea and vomiting is in response to moderately emetic chemotherapy.

16. The method according to claim 12, wherein the administering is intravenous.

17. A method for treating nausea and vomiting in a subject in need thereof comprising administering to the subject the pharmaceutical emulsion according to claim 8.

18. The method according to claim 17, wherein the nausea and vomiting is chemotherapy induced nausea and vomiting.

19. The method according to claim 18, wherein the chemotherapy induced nausea and vomiting is in response to highly emetic chemotherapy.

20. The method according to claim 18, wherein the chemotherapy induced nausea and vomiting is in response to moderately emetic chemotherapy.

21. The method according to claim 17, wherein the administering is intravenous.

Electronic Acknowledgement Receipt

EFS ID:	25324310
Application Number:	15083071
International Application Number:	
Confirmation Number:	9469
Title of Invention:	EMULSION FORMULATIONS OF APREPITANT
First Named Inventor/Applicant Name:	Thomas B. Ottoboni
Customer Number:	108547
Filer:	Susan L. Harlocker/Julie Costello
Filer Authorized By:	Susan L. Harlocker
Attorney Docket Number:	092459-0180/8027.US01
Receipt Date:	28-MAR-2016
Filing Date:	
Time Stamp:	19:20:39
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$3050
RAM confirmation Number	5201
Deposit Account	505907
Authorized User	HARLOCKER, SUSAN

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 CFR 1.17 (Patent application and reexamination processing fees)

Charge any Additional Fees required under 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	Oath or Declaration filed	092459_0180_decs.pdf	167556 7d4b60c9132ba957143cb21bc24981f0d001b400	no	2
Warnings:					
Information:					
2	TrackOne Request	092459_0180_req_prior_exam.pdf	81188 0a489e5f186e31223bf23812595e8fe0a9d1a16f	no	1
Warnings:					
Information:					
3	Application Data Sheet	092459_0180_ads.pdf	459132 93ba84d488335cb4d7d64ec58041e4917670a6f5	no	7
Warnings:					
Information:					
This is not an USPTO supplied ADS fillable form					
4		092459_0180_con_appln.pdf	2104406 65792fc1bc4ef911289edcafdd200c2922f0e9ef	yes	35

Multipart Description/PDF files in .zip description

Document Description	Start	End
Specification	1	31
Claims	32	34
Abstract	35	35

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
Warnings:					
Information:					
5	Drawings-only black and white line drawings	092459_0180_figs.pdf	988668 af3a5c444a4d6417106e2f9d1399950d285fab2e	no	4
Warnings:					
Information:					

6	Fee Worksheet (SB06)	fee-info.pdf	43404 20a840f734fe7c286dde12fc287d1f0459ff4391	no	2

Warnings:

Information:

Total Files Size (in bytes):	3844354

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

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.
15/083,071	03/28/2016	Thomas B. Ottoboni	092459-0180/8027.US01	9469

108547 7590 06/03/2016
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
06/03/2016	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. 15/083,071	Applicant(s) OTTOBONI ET AL.	
	Examiner MIRIAM A. LEVIN	Art Unit 1613	AIA (First Inventor to File) 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 *March 28, 2016*.

☐ 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 *18 May 2016*; 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) *1-21* is/are pending in the application.

5a) Of the above claim(s) *12-21* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-11* is/are rejected.

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

9)☒ Claim(s) *1-21* 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 *March 28, 2016* 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: _____.

1. 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

1. The present application is being examined under the pre-AIA first to invent provisions.

DETAILED ACTION

2. Applicant's application filed March 28, 2016 has been received and entered.

Status of Claims

3. Claims Pending: 1 - 21
4. New claims: N/A
5. Amended claims: none
6. Canceled Claims: none
7. Withdrawn claims: 12-21
   a. Rejoinder was requested (telephonic at time of election)

8. Change in Dependency: none
9. Claims under examination: 1 – 11

10. Elected species: N/A

11. Objections/Rejections withdrawn: N/A

12. Rejections maintained with revision: N/A

13. Rejections necessitated by amendment / New Grounds:
    b. 35 USC 103 over Zhou + Bromer vs. cl. 1 - 12
    c. NSDP vs. 14/859013

14. Terminal Disclaimers: None

15. The following rejections constitute the complete set of rejections presently being applied to the instant application.

Election/Restrictions

16. Restriction to one of the following inventions is required under 35 U.S.C. 121:

    I. Claims 1 - 11, drawn to an injectable pharmaceutical emulsion, classified in A61K 31/5377 and A61K 9/107.

    II. Claims 12 - 21, drawn to a method of treatment, classified in A61K 31/5377 and A61K 9/0019.

17. The inventions are distinct, each from the other because of the following reasons:

18. Inventions I and II are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product. See MPEP § 806.05(h). In the instant case the process of treating nausea and vomiting can be practiced with other drugs (e.g. ondansetron) or with the same active ingredient, aprepitant, in a different formulation which is not an emulsion. (Re: use of aprepitant, note, e.g. background section of instant application.)

19. Restriction for examination purposes as indicated is proper because all these inventions listed in this action are independent or distinct for the reasons given above and there would be a serious search and/or examination burden if restriction were not required because one or more of the following reasons apply:

> The species or groupings of patentably distinct species require a different field of search (e.g. searching different class/subclasses or electronic resources, or employing different search strategies or search queries).

20. **Applicant is advised that the reply to this requirement to be complete must include (i) an election of an invention to be examined** even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected invention**.

21. The election of an invention may be made with or without traverse. To reserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the restriction requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable upon the elected invention.

22. Should applicant traverse on the ground that the inventions are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the inventions to be obvious

variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103 or pre-AIA 35 U.S.C. 103(a) of the other invention.

23. During a telephone conversation with Susan Harlocker on May 18, 2016 a provisional election was made without traverse to prosecute the invention of Group I, claims 1 - 11. Affirmation of this election must be made by applicant in replying to this Office action. Claims 12 – 21 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

24. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be corrected in compliance with 37 CFR 1.48(a) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. A request to correct inventorship under 37 CFR 1.48(a) must be accompanied by an application data sheet in accordance with 37 CFR 1.76 that identifies each inventor by his or her legal name and by the processing fee required under 37 CFR 1.17(i).

25. The examiner has required restriction between product or apparatus claims and process claims. Where applicant elects claims directed to the product/apparatus, and all product/apparatus claims are subsequently found allowable, withdrawn process claims that include all the limitations of the allowable product/apparatus claims should be considered for rejoinder. All claims directed to a nonelected process invention must include all the limitations of an allowable product/apparatus claim for that process invention to be rejoined.

26. In the event of rejoinder, the requirement for restriction between the product/apparatus claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103 and 112. Until all claims to the elected product/apparatus are found allowable, an otherwise proper restriction requirement between product/apparatus claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowable product/apparatus claim will not be rejoined. See MPEP § 821.04. Additionally, in order for rejoinder to occur, applicant is advised that the process claims

should be amended during prosecution to require the limitations of the product/apparatus claims. **Failure to do so may result in no rejoinder.** Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. **See MPEP § 804.01.**

Claim Rejections - 35 USC § 103

27. 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.

28. 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.

29. Claims 1 – 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over (Zhou et al. (CN 102379845 A; published March 21, 2012; cited on IDS), in view of Bromer et al. (US 2007/0071777 A1).

30. 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).

31. Applicant claims an injectable pharmaceutical emulsion comprising:

d. 0.4 – 1.0 wt. % aprepitant;

e. 13 – 15 wt. % egg yolk lecithin;

f. 9 – 10 wt. % soybean oil;

g. Sodium oleate (to adjust pH);

h. Wherein the emulsion has a pH of 7.5 – 9.0.

32. The composition may further comprise 3 - 8 wt. % sucrose and 2 - 6 wt. % ethanol. (e.g. cl. 4 – 8)

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

33. Zhou et al. teach aprepitant microemulsion for injection and preparation method thereof. (title) The emulsion comprises, for example:

i. 0.5 - 2.0 wt. % aprepitant, preferably 1.0 - 1.5 wt. %;

j. 5 – 30 wt. % oil, preferably 7 – 15 wt. % oil, wherein the oil is soybean oil;

k. 0.5 – 10 wt. % emulsifier; preferably 8 – 10 wt. %, wherein the emulsifier is egg yolk phospholipids;

l. 1 – 10 wt. % co-emulsifier, preferably 2 – 5 wt. %, wherein the co-emulsifier is ethanol;

m. 5 – 20 wt. % of a protective agent, preferably 8 – 13 wt. %, wherein the protective agent may be glycerin, sucrose or glucose;

n. 60 – 80 wt. % water, preferably 60 – 69 wt. %;

o. Wherein the pH of the microemulsion is 6.0 - 8.0.

p. (See, e.g. cl. 1, 5 – 9; [0008] – [0011]; see also examples).

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

34. The difference between the instant application and Zhou et al. is that Zhou et al. do not expressly teach using sodium oleate to adjust the pH. This deficiency in Zhou et al. is cured by the teachings of the Bromer et al.

35. Bromer et al. teach an oil emulsion for postnatal hormone substitution (title). The composition may be administered intravenously and may be administered to premature babies. (abs.) An example of the composition comprises soybean oil, egg yolk lecithin (phospholipids), glycerol, water and sodium

oleate. (e.g. [0059], Table 1; see also, e.g., [0037], [0047], [0058]). The pH is adjusted to 6.0 to 9.0 and sodium oleate may be used to adjust the pH of the oil in water emulsion. (e.g. [0053], [0058])

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

36. 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**,** as suggested by Zhou et al. and Bromer et al., and produce the instant invention.

37. One of ordinary skill in the art would have been motivated to do this because Zhou et al. do not recite any particular agent as preferred for adjusting the pH, therefore any suitable compounds may be used. In the absence of unexpected results or other evidence to the contrary, the selection of sodium oleate is the mere selection of a material suitable for the intended use. (MPEP 2144.07)

38. As a second motivation, it is well known in chemistry that use of buffer solutions can provide a more stable or resilient pH. Buffer solutions are formed by using both acid and base, or the salt of an acid. Sodium oleate is the acid salt of oleic acid and sodium hydroxide. Soybean oil contains oleic acid, therefore by using sodium oleate to adjust the pH of the composition, a buffered solution (emulsion) is obtained. This provides additional motivation for the selection of sodium oleate, and assurance of predictable results.

39. As further motivation, and assurance of predictable results / reasonable expectation of success: the composition of Bromer is an oil-in-water emulsion, as is the one of Zhou. Both comprise soybean oil and egg yolk lecithin and both compositions may be injected; the composition of Bromer may be injected in infants. Because both compositions are oil-in-water emulsions, both use similar aqueous phases (glycerol and water), oil phases (soybean oil) and emulsifiers (egg yolk lecithin); and both are intended for use as injectable compositions, use of the same pH adjuster (sodium oleate) is an obvious option and, because of the similarity in the compositions, there is a reasonable expectation of success.

40. The following motivations apply:

2141>Examination Guidelines for Determining Obviousness Under < 35 U.S.C. 103 [R-6]**

III. RATIONALES TO SUPPORT REJECTIONS UNDER 35 U.S.C. 103

(A)Combining prior art elements according to known methods to yield predictable results;
(B)Simple substitution of one known element for another to obtain predictable results;
(E) "Obvious to try" – choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success;
(G)Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention.

41. In regard to all of the other ingredients, Zhou et al. teach each of them and teach using almost of all of them in ranges that touch, border on, overlap or are close to the instantly claimed ranges and therefore anticipate and/or render obvious the instantly claimed ranges.

42. The only ingredient recited in the instant claims with a range that does not at least touch the range taught by Zhou et al. is that of the emulsifier. Zhou teaches 0.5 – 10 wt. % emulsifier; preferably 8 – 10 wt. %, wherein the emulsifier is egg yolk phospholipids. The instant claims recite 13 - 15 wt. % egg yolk lecithin. However, it is not clear that this slight variation will make any difference in the properties of the composition and is therefore routine optimization.

2131.03Anticipation of Ranges [R-6]

I. A SPECIFIC EXAMPLE IN THE PRIOR ART WHICH IS WITHIN A CLAIMED RANGE ANTICIPATES THE RANGE

"[W]hen, as by a recitation of ranges or otherwise, a claim covers several compositions, the claim is 'anticipated' if *one* of them is in the prior art." *Titanium Metals Corp. v. Banner,* 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985) (citing *In re Petering*, 301 F.2d 676, 682, 133 USPQ 275, 280 (CCPA 1962)) (emphasis in original)

2144.05 Obviousness of Ranges [R-5]

I. OVERLAP OF RANGES

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, 191USPQ 90 (CCPA 1976) . . . Similarly, a *prima facie* case of obviousness exists where the claimed ranges and prior art ranges do not overlap but are close enough that one skilled in the art would have expected them to have the same properties. *Titanium Metals Corp. of America v. Banner*, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985) . . .

Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ. It would have been customary for an artisan of ordinary skill to determine the optimal wt. % of emulsifier needed to achieve the desired results. Thus, absent some

demonstration of unexpected results from the claimed parameters, the optimization of the wt. % of emulsifier would have been obvious at the time of Applicant's invention.

43. Claims 1- 11 are rejected.

44. 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).

45. 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

46. 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 claims at issue 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); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

47. 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 a nonstatutory double patenting ground provided the reference application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

48. The USPTO internet Web site contains terminal disclaimer forms which may be used. Please visit http://www.uspto.gov/forms/. The filing date of the application will determine what form 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 http://www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

49. Claims 1 – 21 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1 – 13 and 18 - 20 of copending Application No. 14/859013 (the '013). Although the claims at issue are not identical, they are not patentably distinct from each other because instant claims 1 - 11 recite a composition comprising 0.4 - 1.0 wt. % aprepitant, 13 - 15 wt. % egg yolk lecithin, 9 - 10 wt. % soybean oil, sodium oleate as a pH modifier, a pH of 7.5 - 9.0; 3 – 8 wt. % sucrose and 2 – 6 wt. % ethanol, and narrower ranges falling within these (cl. 1 - 11). The instant claims also recite a method for treating nausea and vomiting, due, e.g. to chemotherapy, comprising administering the composition of claim 1, e.g. intravenously (cl. 12 - 21).

50. The copending claims recite a composition comprising aprepitant wherein the composition contains 11 - 15 wt. % of an emulsifier (cl. 1), e.g. egg lecithin (cl. 1, 5, 7); a ratio of 15:1 - 30:1 (wt. %) of emulsifier to aprepitant in the oil phase (so about 0.3 - 1.0 wt. % aprepitant) (cl. 3), a ratio of 1:1 to 3:1 (wt. %) of emulsifier to oil (so about 4 – 15 wt. %) (cl. 4; note also cl. 2, ratio to aprepitant); pH modifier is sodium oleate (cl. 9) and the pH is 7.5 – 9.0 (cl. 1), addition of buffer, etc. are permitted due to "comprising" language (cl. 6, 8, 10); ethanol is less than 10 wt. % (cl. 12, 1); oil is soybean oil (cl. 11). Claim 1 recites a tonicity modifier; p. 15 of the specification for the '013 gives examples of tonicity agents, including sucrose, mannitol, glycerin or dextrose, or a mixture thereof, and p. 16 gives examples of appropriate amounts to use, e.g. 0 - 20 wt. % sucrose. (p. 15, section 2. Aqueous phase, [0091]; see also p. 16, [0094] – sucrose used in 0 - 30 %, 0 - 25 % or 0 - 20 %) Therefore use of 0 – 20 % sucrose is obvious.

51. In regard to the difference in ranges:

2144.05 Obviousness of Ranges [R-5]

I. OVERLAP OF RANGES

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, 191USPQ 90 (CCPA 1976) . . . Similarly, a *prima facie* case of obviousness exists where the claimed ranges and prior art ranges do not overlap but are close enough that one skilled in the art would have expected them to have the same properties. *Titanium Metals Corp. of America v. Banner*, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985) (Court held as proper a rejection of a claim directed to an alloy of "having 0.8% nickel, 0.3%molybdenum, up to 0.1% iron, balance titanium" as obvious over a reference disclosing alloys of 0.75%nickel, 0.25% molybdenum, balance titanium and 0.94%nickel, 0.31% molybdenum, balance titanium.).

52. In regard to the method of using the composition, the copending claims recite a method of treating a patient with emesis, which may be induced by chemotherapy, comprising administering the composition of claim 1. While injection is not specifically recited, it is a known method of administering a drug, and is suitable for use when the patient has emesis or nausea. If the patient is just going to vomit up the medication, the medication can't help the patient; therefore injection is a reasonable alternative mode of administration.

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

Conclusion

Claims 1 - 11 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).

/M. A. L./

Examiner, Art Unit 1613

/ANNA PAGONAKIS/

Primary Examiner, Art Unit 1628

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/083,071	03/28/2016	Thomas B. Ottoboni	092459-0180/8027.US01	9469

108547 7590 08/31/2016
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
08/31/2016	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

Applicant-Initiated Interview Summary	Application No.	Applicant(s)	
	15/083,071	OTTOBONI ET AL.	
	Examiner	Art Unit	
	MIRIAM A. LEVIN	1613	

All participants (applicant, applicant's representative, PTO personnel):

(1) *MIRIAM A. LEVIN*.

(2) *Dr. Susan Harlocker, patent agent*.

(3) *Dr. Tom Ottoboni, named inventor, Sr. VP R&D*.

(4)_____.

Date of Interview: *25 August 2016*.

Type: ☒ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☒ No.
If Yes, brief description: _____.

Issues Discussed ☐101 ☐112 ☐102 ☒103 ☐Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: *1*.

Identification of prior art discussed: *Zhou (cited in office action)*.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

See Continuation Sheet.

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☒ Attachment

/ANNA PAGONAKIS/
Primary Examiner, Art Unit 1628

Summary of Record of Interview Requirements

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Paragraph (b)

In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

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The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

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- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

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2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
   (The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiner's version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, "Interview Record OK" on the paper recording the substance of the interview along with the date and the examiner's initials.

Continuation of Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: Agreement: Applicant does not need to amend the claims to recite functional limitations. The Examiner will issue this interview summary and Applicant will file a response.

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The Examiner noted that Zhou [0012] and [0013] appear to indicate a particle size of 50 - 150 nm. Dr. Ottoboni advised that this is a starting point for an injectable composition per USP (United States Pharmacopeia) and that this appears to refer to the size of the lipid droplet in Zhou. Dr. Ottoboni noted that with aprepitant, the crystals form on the outside of the lipid droplets. (Photographs were filed as drawings for this case, but it is hard to see fine details on the photographs.) The Examiner noted that Zhou teaches that aprepitant is not soluble in water or organic solvent. [0017]

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Dr. Ottoboni noted that Zhou uses a typical drug lipid solution where one optimizes the amount of oil. In comparison, Applicant found that the amount of emulsifier vs. drug is more important for this drug.

As Dr. Ottoboni explained the chemistry behind the invention: Aprepitant is a NK1 inhibitor. It contains fluorocarbon with florinated phenyl groups, which are hydrophobic. Aprepitant also has amine and amide groups, as well as oxygens, which are hydrophilic. Therefore aprepitant is kind-of a "hydrid" compound. It is neither hydrophobic nor hydrophilic; parts of the molecular are hydrophobic while other parts are hydrophilic. Aprepitant was found to be best solubilized in the emulsifier, rather than in aqueous phase or oil phase. So optimizing the amount of emulsifer vs. drug content is important.

The Examiner advised that Applicant's arguments and evidence appear to show criticality of the claimed range for the emulsifier and criticality of the ratio of aprepitant to emulsifier. Unless the Examiner finds 102 art, the Examiner believes this evidence and arguments will over come most 103 rejections. The Examiner will need to conduct a follow up search and therefore cannot promise that the claims are allowable at this point.

Attorney Docket No. 092459-0180/8027.US01

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF:	OTTOBONI ET AL.	EXAMINER:	LEVIN, MIRIAM A.
APPLICATION NO.:	15/083,071	ART UNIT:	1613
FILED:	MARCH 28, 2016	CONF. NO:	9469
FOR:	EMULSION FORMULATIONS OF APREPITANT		

Discussion Points for Telephonic Interview

Not for Entry to the Record

1. Interview scheduled for 2:00 p.m. EST / 11:00 a.m. PST on Thursday August 25, 2016.

   Applicants' representative will call Examiner Levin at:

   571-270-3471

2. PARTICIPANTS

   Dr. Susan Harlocker, Patent Agent for Applicants

   Dr. Tom Ottoboni, named inventor, Senior V.P. Pharmaceutical and Preclinical R&D, Heron Therapeutics, Inc.

3. **Claim 1**

   Claim 1 is directed to an injectable pharmaceutical emulsion.

	Claim 1	**Zhou et al. (per Office Action)**
Aprepitant	0.4 – 1.0 wt/wt%	0.5-2.0 / 1.0-1.5 wt/wt%
Emulsifier: Egg yolk lecithin/phospholipid	13-15 wt/wt%	0.5-10/8-10 wt/wt%
Soybean oil	9-10 wt/wt%	5-30/7-15 wt/wt%
Sodium oleate	pH modifier	Not present
pH	7.5 – 9.0	6-8

4. Claims 1-11 Rejected as Obvious Over Zhou et al. (CN 102379845) in View of Bromer (US 2007/0071777)

   The Examiner's Position

   - Zhou describes an aprepitant emulsion for injection comprising 0.5-10 or 8-10 wt/wt% emulsifier, compared to 13-15 wt/wt% for the presently claimed pharmaceutical emulsion.

PAGE 1/2 * RCVD AT 8/24/2016 1:02:20 PM [Eastern Daylight Time] * SVR:W-PTOFAX-002/38 * DNIS:2704471 * CSID: * DURATION (mm-ss):00-46

- The only ingredient recited in the instant claims with a range that does not at least touch the range taught by Zhou et al. is that of the emulsifier.
- "It is not clear that this slight variation will make any difference in the properties of the composition and is therefore routine optimization."
- Zhou does not expressly teach sodium oleate to adjust the pH. This deficiency is cured by the teachings of Bromer which teaches adjusting an emulsion of postnatal hormone substitution using sodium oleate.

Legal Basis for the Rejection:

- Obvious to determine the optimal wt% of emulsifier to achieve the desired results absent some demonstration of unexpected results from the claimed parameters.
- In the absence of unexpected results, the selection of sodium oleate as taught by Bromer is the mere selection of a material for the intended use.

Applicant's Rebuttal:

- An emulsifier present in a range of 13-15 wt/wt% unpredictably and unexpectedly results in a pharmaceutical emulsion which is more stable (e.g., lack of crystal formation) than an aprepitant emulsion with 0.5-10 or 8-10 wt/wt% emulsifier as taught by Zhou.
- The emulsion of Bromer comprises an emulsifier content from about 0.6 to 1.5 wt% (paragraph [0047])
- Use sodium oleate to adjust the pH of the emulsion would not be obvious in view of Bromer because the problem of emulsion stability was not recognized by Zhou or Bromer and the effect of oleate on stability of an emulsion comprising 13-15 wt/wt% emulsifier was not predictable.

UNITED STATES PATENT AND TRADEMARK OFFICE

Facsimile Transmission

To:	**Name:**	Dr. Susan Harlocker
	Company:	McDermott Will & Emery
	Fax Number:	650-815-7401
	Voice Phone:	650-815-7647
From:	**Name:**	Miriam Levin
	Voice Phone:	571.270.3471

37 C.F.R. 1.6 sets forth the types of correspondence that can be communicated to the Patent and Trademark Office via facsimile transmissions. Applicants are advised to use the certificate of facsimile transmission procedures when submitting a reply to a non-final or final Office action by facsimile (37 CFR 1.8(a)).

Fax Notes:

Dr. Harlocker,

This is my recollection of our interview today. Please advise if any correction is needed. Thank you.

Asst. Ex. Miriam Levin

Date and time of transmission: Thursday, August 25, 2016 5:07:12 PM
Number of pages including this cover sheet: 05

Applicant-Initiated Interview Summary	Application No.	Applicant(s)	
	15/083,071	OTTOBONI ET AL.	
	Examiner	Art Unit	
	MIRIAM A. LEVIN	1613	

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(2) *Dr. Susan Harlocker, patent agent*.

(3)*Dr. Tom Ottoboni, named inventor, Sr. VP R&D*.

(4)_____.

Date of Interview: *25 August 2016*.

Type: ☒ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☒ No.
If Yes, brief description: _____.

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5) a brief identification of the general thrust of the principal arguments presented to the examiner,
   (The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiner's version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, "Interview Record OK" on the paper recording the substance of the interview along with the date and the examiner's initials.

Applicant-Initiated Interview Summary	Application No.	Applicant(s)	
	15/083,071	OTTOBONI ET AL.	
	Examiner	Art Unit	
	MIRIAM A. LEVIN	1613	

All participants (applicant, applicant's representative, PTO personnel):

(1) *MIRIAM A. LEVIN*.

(2) *Dr. Susan Harlocker, patent agent*.

(3)*Dr. Tom Ottoboni, named inventor, Sr. VP R&D*.

(4)_____.

Date of Interview: *25 August 2016*.

Type: ☒ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☒ No.
If Yes, brief description: _____.

Issues Discussed ☐101 ☐112 ☐102 ☒103 ☐Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: *1*.

Identification of prior art discussed: *Zhou (cited in office action)*.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc..)

See Continuation Sheet.

Applicant recordation instructions: The formal written reply to the last Office action must include the substance of the interview. (See MPEP section 713.04). If a reply to the last Office action has already been filed, applicant is given a non-extendable period of the longer of one month or thirty days from this interview date, or the mailing date of this interview summary form, whichever is later, to file a statement of the substance of the interview

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☒ Attachment

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**	

AMENDMENT UNDER 37 C.F.R. § 1.111

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

Sir:

The present communication responds to the non-final Office Action dated June 3, 2016 in the above-identified application.

Remarks begin on page 2.

REMARKS

Reconsideration and withdrawal of the rejections set forth in the non-final Office Action dated June 3, 2016 are respectfully requested.

I. Interview Summary

Applicants thank Examiner Levin for the interview (hereinafter, "Examiner Interview") which took place on August 25, 2016. Also participating were the undersigned and inventor Dr. Thomas Ottoboni. Compliant with M.P.E.P. § 713.04 Applicants provide this summary of the interview.

During the interview, participants discussed the § 103 rejection, differences between the claimed subject matter and the cited primary reference, and the basis for Applicants' position that the presently claimed pharmaceutical emulsion is not obvious over the cited references at least because the claimed emulsion represents a showing of unexpected results which is sufficient to rebut the obviousness rejection.

Additional details of the interview are set forth in Applicants' response to the rejection under 35 U.S.C. § 103(a).

II. Status of the Claims

Claims 1-21 are pending. Claims 1-11 are presently under examination. Claims 12-21 are withdrawn.

III. Restriction Requirement

During a telephone conversation with Examiner Levin on May 18, 2016, Applicants' representative was requested to elect a group for examination. Examiner Levin asked Applicants to choose between Group I, claims 1-11, directed to an injectable pharmaceutical emulsion, and Group II, claims 12-21, directed to a method of treatment. Applicants elected Group I, claims 1-11, without traverse. Claims 1-11 read on the elected Group.

IV. Rejections Under 35 U.S.C. § 103

Claims 1-11 were rejected under 35 U.S.C. §103 (a) as allegedly being unpatentable over Zhou et al., CN102379845A, published March 21, 2012 (hereinafter "Zhou") in view of Bromer et al. (U.S. Patent Publication No. 2007/0071777A1, "hereinafter "Bromer").

A. The Cited Art

ZHOU is a published Chinese patent application. A translation of the application was provided by Applicants in the Information Disclosure Statement filed for the instant application on April 12, 2016 Zhou describes oil-in-water emulsions of aprepitant.

BROMER describes oil-in-water emulsions of estrogen and progesterone and is cited by the Examiner for its teaching of using sodium oleate to modify the pH of the emulsion.

The present claims are directed to a pharmaceutical emulsion comprising 0.4 to 1.4 wt% aprepitant, 13 to 15 wt% egg yolk lecithin, 9 to 10 wt% soybean oil, and a pH modifier which is soldium oleate. The pH of the pharmaceutical emulsion is 7.5 to 9.0. Zhou is cited as the primary reference for teaching 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.

The Examiner notes that Zhou does not teach the use of sodium oleate as a pH modifier and relies on Bromer for teaching sodium oleate to modify the pH of an oil emulsion of postnatal hormone substitutes. Specifically, the Examiner states that one of ordinary skill in the art would have been motivated to use sodium oleate as taught by Bromer to adjust the pH of the emulsion because Zhou does not recite any particular agent as preferred for adjusting the pH, and therefore any suitable compounds may be used.

The Examiner also notes that aside from the pH modifier, Zhou teaches each of the other ingredients recited in the present claims using almost all of them in ranges that touch, border on, overlap or are close to the instantly claimed ranges. The Examiner states 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 instant claims recite 13 to 15 wt% egg yolk lecithin while Zhou teaches 0.5 to 10 wt%, preferably 8 to 10 wt% emulsifier wherein the emulsifier is egg yolk lecithin.

The rejection is traversed for the following reasons.

B. The Legal Standard

An invention "composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art. *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 418 (2007). "Often, it will be necessary...to look to interrelated teachings of multiple [references]....and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known element in the fashion claimed[.]" *Id.* "[T]his analysis should be made explicit," and it "can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." *Id.* "We must still be careful not to allow hindsight reconstruction of references to reach the claimed invention without any explanation as to how or why the references would be combined to produce the claimed invention." *Innogenetics, N.V. v. Abbott Labs.*, 512 F.3d 1363, 1374 n.3 (Fed. Cir. 2008).

In order to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be an apparent reason why a person of ordinary skill would have combined the prior art elements in the manner claimed. *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991). Second, there must be a reasonable expectation of success. Third, the references when combined, must teach or suggest all the claim limitations. *Id.; Procter & Gamble Co. v. Teva Pharmaceuticals USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009); *see also M.P.E.P. § 2143.*

To sustain a *prima facie* case of obviousness, the Examiner must prevail on all three criteria. A failure on any one precludes a finding of *prima facie* obviousness. As will be articulated hereinbelow, the present rejection cannot be sustained because none of the elements has been satisfied.

According to the M.P.E.P. § 2143 I. A., the rationale to support a conclusion that the claim would have been obvious is that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination yielded nothing more than predictable results to one of ordinary skill in the art. *KSR*, 550 U.S. at 416, 82USPQ2d at 1395; *Sakraida v. AG Pro, Inc.*, 425U.S. 273, 282, 189 USPQ 449, 453 (1976); *Anderson's-Black Rock, Inc. v. Pavement Salvage Co.*, 396 U.S. 57, 62-63, 163 USPQ 673, 675 (1969); *Great Atl. & P. Tea Co. v. Supermarket Equip.Corp.*, 340 U.S. 147, 152, 87 USPQ 303, 306 (1950)."[I]t can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." *KSR*, 550 U.S. at418, 82

USPQ2d at 1396. If any of these findings cannot be made, then this rationale cannot be used to support a conclusion that the claim would have been obvious to one of ordinary skill in the art.

As stated in the M.P.E.P. § 2144.09 VII, a *prima facie* case of obviousness based on structural similarity is rebuttable by proof that the claimed compounds possess unexpectedly advantageous or superior properties. *In re Papesch,* 315 F.2d 381, 137 USPQ43 (CCPA 1963).

C. Reasons to Combine the Elements of the Cited Art Were Not Known

The obviousness rejection is based largely on the Examiner's assertion that it would have been customary for an artisan of ordinary skill to determine the optional weight percent of emulsifier needed to achieve the desired results. The Examiner then states that absent some demonstration of unexpected results from the claimed parameters, the optimization of the weight percent of emulsifier would have been obvious at the time of Applicants' invention.

As discussed during the Examiner Interview, Applicants assert that the instant claims represent identification of a problem not previously recognized by Zhou or Bremer. Specifically, the claimed pharmaceutical emulsion comprising in part 0.4 to 1.0 wt/wt% aprepitant, 13 to 15 wt/wt% egg yolk lecithin, and 9 to 10 wt/wt% soybean oil (e.g., Examples 1, 2, and 6), is pharmaceutically stable for at least the reasons that crystals do not form in the claimed pharmaceutical emulsion after storage for more than, e.g., 4 days at room temperature. As shown in Table 7 on pages 27-28 of the instant specification as filed, the formulations of Examples 1, 2, 3 and 6 were 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, 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 less than 13 wt/wt% egg yolk lecithin (9.95 wt/wt% Lipoid E 80), 0.672 wt/wt% aprepitant and 8.96 wt/wt% soybean oil resulted in an emulsion in which crystals were observed within 4 days post preparation at room temperature.

In the absence of any evidence that a person having ordinary skill in the art (POSA) at the time of filing knew that the aprepitant emulsions taught by Zhou lacked stability, there is no basis for concluding that the present claims would have been obvious over the cited art for at least the reason that there was no motivation to combine the references. Neither Zhou nor Bromer

recognizes the formation of crystals in the emulsions produced as described in each of their references or the effects of 13 to 15 weight percent emulsifier on stability of an emulsion.

D. The Claimed Pharmaceutical Emulsions Possess Unexpected Results and Advantages

Applicants assert that stability (e.g., the lack of crystal formation) of aprepitant emulsions resulting from a formulation comprising *inter alia* 0.4 to 1.0 wt/wt% aprepitant and 13 to 15 wt/wt% egg yolk lecithin demonstrates an unexpected and unpredictable advantage of the claimed pharmaceutical emulsions over the aprepitant formulations of Zhou. Bromer does not cure the defects of Zhou for at least the reason that the formulations of Bromer do not comprise 13 to 15 wt/wt% emulsifier or 0.4 to 1.0 wt/wt% aprepitant. Applicants note that the aprepitant pharmaceutical emulsions generated as described in Examples 1, 2, 3, and 6 have emulsifier weight percentages ranging from 11.7 to 14.3, which fall outside the range of emulsifier weight percent taught by Zhou. None of the emulsions described in Examples 1, 2, 3, and 6 of the instant application showed crystal formation prior to 2 or 3 months storage at room temperature. Examples 4 and 5 contain 9.95 and 2.5 weight percent emulsifier, respectively, and the resultant emulsion of both formed crystals within 4 days of storage at room temperature. Nothing in Zhou or Bremer recognizes the problem of crystal formation in the aprepitant formulations, accordingly, nothing in Zhou or Bremer provides the motivation or guidance for altering the weight percent of emulsifier to arrive at the instantly claimed formulations.

As noted in the Interview Summary by the Examiner mailed August 31, 2016 (hereinafter, "Examiner Interview Summary"), the Examiner requested clarification regarding the differences between the emulsion preparation process described in Example 4 of the instant specification and the emulsion preparation process described in the examples of Zhou. The Examiner questioned whether the unexpected results (e.g., increased stability) was due to a difference in the method of preparing the emulsion. As suggested by the Examiner, Applicants provide with this response a Declaration by Dr. Ottoboni describing the process of emulsion preparation by Zhou and comparing it to the emulsion preparation described in the instant specification. In the Declaration (attached as Exhibit A), Dr. Ottoboni confirms that Example 4 describes an emulsion that was prepared according to the methods taught by Zhou.

During the Examiner Interview, the Examiner also questioned a possible difference in the

method of generating the formulation per Zhou (or Example 4 of the instant application) as compared to Examples 1, 2, 3, and 6 in the instant application for preparing the claimed pharmaceutical emulsions. The Examiner noted that both Example 4 of the instant application and Zhou describe adding ethanol a second time when the oil was added to the mixture of aprepitant and emulsifier. As noted in the Examiner Interview Summary, Dr. Ottoboni directed the Examiner to Example 5 of the instant application. The emulsion of Example 5 shows an initial mixing of aprepitant, egg yolk phospholipid, soybean oil, and oleic acid followed by the addition of ethanol to dissolve the mixture at 70°C. No second step of ethanol addition is performed. As summarized in the Examiner Interview Summary, the emulsion prepared in Example 5 uses a lower weight percent of emulsifier (2.5 wt%). Without being bound by theory, Applicants note that the ratio of emulsifier to aprepitant was lower in both Example 4 and 5 when compared to the other examples. This difference of emulsifier:drug ratio, reflected in the claimed ingredient ranges, may contribute significantly to crystal formation in the aprepitant emulsions.

To summarize the arguments provided above, Applicants submit that the present claims are not obvious over Zhou in view of Bromer for at least the reasons that the Examiner has not identified a reason that would have prompted a POSA in the relevant filed to combine elements and ranges in a way the present claims do and the claimed compositions possess unexpected and unpredictable advantages over the cited art as evidenced by the increased stability of the claimed pharmaceutical emulsions.

Accordingly, Applicants respectfully request withdrawal of the rejections under 35 U.S.C. §103.

V. Double Patenting

Claims 1-21 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-13 and 18-20 of co-pending Application Serial No. 14/859,013.

Applicants herein submit a Terminal Disclaimer in accordance with 37 C.F.R. § 1.321(b) and (c), thereby obviating the above obviousness type double patenting rejections over co-pending Application Serial No. 14/859,013.

VI. Conclusion

No additional fees are believed due with this communication. However, the Commissioner is hereby authorized and requested to charge any deficiency in fees herein to Deposit Account No. 50-5907.

If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to contact the undersigned at (650) 815-7647.

Respectfully submitted,

Date: September 1, 2016

/Susan L. Harlocker/
Susan L. Harlocker
Registration No. 59,144

Correspondence Address:
Customer No. 108547

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 2010
Date

Thomas Ottoboni, Ph.D.

APPENDIX A

Thomas Ottoboni Ph.D.

Professional Profile

- Ph.D. in organic chemistry with a broad scientific background and a registered patent agent.
- Conceived and developed multiple product technology platforms in the pharmaceutical and medical device fields.
- Extensive experience in pharmaceutical and medical device development with hands-on roles in all aspects of R&D, manufacturing, quality, regulatory affairs, and intellectual property management.

Education

- Ph.D. Chemistry. University of California, Berkeley, 1986. Organic Chemistry
- M.S. Chemistry. San Francisco State University, 1982. Organic Chemistry
- B.S. Chemistry. University of California Berkeley, 1981.

Professional Certification

- Registered to Practice before the USPTO, Reg. No. 64987

US Patents and Applications

8,486,444	Nanobubbles useful as an ultrasonic contrast agent for the lymphatic system
8,460,637	Reconstitutable microsphere compositions useful as ultrasonic contrast agents
6,896,659	Method for ultrasound triggered drug delivery using hollow microspheres.
6,776,761	Hollow microspheres with controlled fragility for medical use
6,524,608	Intravesical drug delivery system
6,482,518	Excipient for the lyophilization of aqueous suspensions of microparticles
6,207,180	Intravesical drug delivery
6,193,951	Microparticles useful as ultrasonic contrast agents
6,039,967	Intravesical drug delivery system
5,977,171	Sustained release emulsions
5,977,044	Liquid peracid precursor colloidal dispersions: macroemulsions
5,837,226	Ocular microsphere delivery system
5,776,877	Liquid peracid precursor colloidal dispersions: macroemulsions
5,767,153	Sustained release emulsions
5,731,005	Hydrogel-based microsphere drug delivery systems
5,710,296	Process for preparing phenyl esters
5,667,735	Opthalmic mold coatings
5,551,663	Plastic molds for ophthalmic devices and methods for forming same
5,459,176	Radiation curable coating for plastic articles
5,415,796	Liquid nonaqueous detergent with stable, solubilized peracid
5,269,962	Oxidant composition containing stable bleach activator granules

20070243138	Hollow microspheres with controlled fragility for medical use
20060241466	Hollow microspheres with controlled fragility for medical use
20050113697	Method of imaging lymphatic system using nanocapsule compositions
20050106105	Methods and compositions for ultrasound imaging of apoptosis
20040185108	Method of preparing gas-filled polymer matrix microparticles useful for delivering drug
20040086459	Microparticles useful as ultrasonic contrast agents
20030215394	Microparticles having a matrix interior useful for ultrasound triggered delivery of drugs into the bloodstream
20030036697	Hollow microspheres with controlled fragility for medical use
20020151792	Method for ultrasound triggered drug delivery using hollow microbubbles with controlled fragility
20010012522	Microparticles useful as ultrasonic contrast agents and for delivery of drugs into the bloodstream
20140161726	Reconstitutable Microsphere Compositions Useful As Ultrasonic Contrast Agents
20140275145	Compositions of a polyorthoester and an aprotic solvent
20140275046	Compositions of a polyorthoester and an aprotic solvent
20140296282	Compositions of a polyorthoester and an aprotic solvent
20150297729	Long-acting polymeric delivery systems
20150297730	Compositions of a polyorthoester and an organic acid excipient
20150320866	Pharmaceutical composition comprising antiemetic compounds and polyorthoester
20160082013	Emulsion formulations of aprepitant
20160206622	Emulsion formulations of aprepitant
20160206761	Reconstitutable Microsphere Compositions Useful As Ultrasonic Contrast Agents

Publications and Presentations

Peer Reviewed Publications

Biochronomer™ technology and the development of APF530, a sustained release formulation of granisetron. Ottoboni T, Gelder M, O'Boyle E., *J Exp Pharmacology*. **2014**, 2014(6), 15-21

Characterization of the in vitro adherence behavior of ultrasound responsive double-shelled microspheres targeted to cellular adhesion molecules. Ottoboni S, Short RE, Kerby MB, Tickner EG, Steadman E, Ottoboni TB., *Contrast Media Mol Imaging*. **2006**, 1(6):279-90.

Sentinel node detection using contrast-enhanced power Doppler ultrasound lymphography. Wisner ER, Ferrara KW, Short RE, Ottoboni TB, Gabe JD, Patel D. *Invest Radiol*. **2003**, 38(6):358-65.

Contrast enhanced intermittent power Doppler ultrasound with sub-micron bubbles for sentinel node detection. Wisner ER, Ferrara K, Gabe JD, Patel D, Nyland TG, Short RE, Ottoboni TB. *Acad Radiol*. **2002**, 9 Suppl 2:S389-91.

Hyperpolarized ^{3}He microspheres as a novel vascular signal source for MRI. Chawla MS, Chen XJ, Cofer GP, Hedlund LW, Kerby MB, Ottoboni TB, Johnson GA. *Magn Reson Med*. **2000**, 43(3):440-5.

Betaine:homocysteine methyltransferase from rat liver: purification and inhibition by a boronic acid substrate analog. Lee KH, Cava M, Amiri P, Ottoboni T, Lindquist RN. *Arch Biochem Biophys*. **1992**, 292(1):77-86.

Organic Reactions Under High Pressure. A Mild Method for the Placement of Protecting Groups on Hindered and Sensitive Alcohols. Dauben, W.G.; Bunce, R.A.: Gerdes, J.M.; Henegar, K.E.: Cunningham. A.F.; Ottoboni, T.B. *Tetrahedron Letters* **1982**, *24*, 5709.

Presentations

Detection of Recent Myocardial Ischemia Using a New Contrast Agent Designed for Human Application. Xiaoping Leng; Jianjun Wang; Carson Andrew; Michelle Grata; Abigail Schwartz; Huili Fu; Linda Lavery; Xucai Chen; Sue Ottoboni; Tom Ottoboni; William R Wagner; Flordeliza S Villanueva. American Heart Association, Annual Scientific Sessions 2010

Fate of Targeted Ultrasound Contrast Agents after Endothelial Adhesion: A Time Course Study. Shivani Bowry; Jianjun Wang; Sue Ottoboni; Tom Ottoboni; William R Wagner; Flordeliza Villanueva. American Heart Association, Annual Scientific Sessions 2007

Targeted Ultrasound Imaging of Apoptosis in Acute Myocardial Injury with Annexin-A5-Microspheres. Verjans JW, Haider N, Li P, Narula N, Brittin R, Gabe J, Ottoboni TB, Hofstra L, Reutelingsperger C, Narula J, Vannan MA. American Heart Association, Annual Scientific Sessions, 2004

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Evaluation of Cardiac Function and Morphology During Myocardial Contrast Echocardiography with Cardiosphere® in Anesthetized Dogs. Goldman, JH; del Balzo; U; Ottoboni, TB. Annual Meeting of the European Society of Cardiology, 2006

Hemodynamic and Toxicology studies of PB127, a double shell ultrasound contrast agent containing nitrogen, Jonathan Goldman, Mary Treuhaft, Edward Koo, Brian Rogers, Roger Culbertson, Jerry Griffin, Thomas Ottoboni. American Heart Association, Annual Scientific Sessions 2002

Perfusion Assessment using Hyperpolarized 3He Microspheres. M.S. Chawla, G.P. Cofer, L.W. Hedlund, J.K. Tajik, M.B. Kerby, T.B. Ottoboni, G.A. Johnson. Scientific Meeting of the International Society for Magnetic Resonance in Medicine 2000

Professional Experience

Heron Therapeutics

Senior Vice President, Preclinical and Pharmaceutical Development	2014-Present
Vice President, Pharmaceutical Development	2012-2014
Independent Consultant to the Pharmaceutical Industry	2008-2010

Point Biomedical Corporation, San Carlos CA

Executive Vice President, Operations	2002-2008
Vice President, Research and Development	1996-2000

bioMosaic Systems, Belmont CA

Founder, President	2000-2001

InSite Vision, Alameda CA

Manager, Systems Development	1994-1996

Soane Technologies, Hayward CA

Project Leader, Materials Development 1993-1994

Vitaphore Corp., Menlo Park CA

Director, Drug Delivery 1991-1993

Senior Chemist

The Clorox Company, Pleasanton CA

Senior Scientist 1986-1991

REMARKS

Reconsideration and withdrawal of the rejections set forth in the non-final Office Action dated June 3, 2016 are respectfully requested.

I. Interview Summary

Applicants thank Examiner Levin for the interview (hereinafter, "Examiner Interview") which took place on August 25, 2016. Also participating were the undersigned and inventor Dr. Thomas Ottoboni. Compliant with M.P.E.P. § 713.04 Applicants provide this summary of the interview.

During the interview, participants discussed the § 103 rejection, differences between the claimed subject matter and the cited primary reference, and the basis for Applicants' position that the presently claimed pharmaceutical emulsion is not obvious over the cited references at least because the claimed emulsion represents a showing of unexpected results which is sufficient to rebut the obviousness rejection.

Additional details of the interview are set forth in Applicants' response to the rejection under 35 U.S.C. § 103(a).

II. Status of the Claims

Claims 1-21 are pending. Claims 1-11 are presently under examination. Claims 12-21 are withdrawn.

III. Restriction Requirement

During a telephone conversation with Examiner Levin on May 18, 2016, Applicants' representative was requested to elect a group for examination. Examiner Levin asked Applicants to choose between Group I, claims 1-11, directed to an injectable pharmaceutical emulsion, and Group II, claims 12-21, directed to a method of treatment. Applicants elected Group I, claims 1-11, without traverse. Claims 1-11 read on the elected Group.

IV. Rejections Under 35 U.S.C. § 103

Claims 1-11 were rejected under 35 U.S.C. §103 (a) as allegedly being unpatentable over Zhou et al., CN102379845A, published March 21, 2012 (hereinafter "Zhou") in view of Bromer et al. (U.S. Patent Publication No. 2007/0071777A1, "hereinafter "Bromer").

A. The Cited Art

ZHOU is a published Chinese patent application. A translation of the application was provided by Applicants in the Information Disclosure Statement filed for the instant application on April 12, 2016 Zhou describes oil-in-water emulsions of aprepitant.

BROMER describes oil-in-water emulsions of estrogen and progesterone and is cited by the Examiner for its teaching of using sodium oleate to modify the pH of the emulsion.

The present claims are directed to a pharmaceutical emulsion comprising 0.4 to 1.4 wt% aprepitant, 13 to 15 wt% egg yolk lecithin, 9 to 10 wt% soybean oil, and a pH modifier which is soldium oleate. The pH of the pharmaceutical emulsion is 7.5 to 9.0. Zhou is cited as the primary reference for teaching 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.

The Examiner notes that Zhou does not teach the use of sodium oleate as a pH modifier and relies on Bromer for teaching sodium oleate to modify the pH of an oil emulsion of postnatal hormone substitutes. Specifically, the Examiner states that one of ordinary skill in the art would have been motivated to use sodium oleate as taught by Bromer to adjust the pH of the emulsion because Zhou does not recite any particular agent as preferred for adjusting the pH, and therefore any suitable compounds may be used.

The Examiner also notes that aside from the pH modifier, Zhou teaches each of the other ingredients recited in the present claims using almost all of them in ranges that touch, border on, overlap or are close to the instantly claimed ranges. The Examiner states 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 instant claims recite 13 to 15 wt% egg yolk lecithin while Zhou teaches 0.5 to 10 wt%, preferably 8 to 10 wt% emulsifier wherein the emulsifier is egg yolk lecithin.

The rejection is traversed for the following reasons.

B. The Legal Standard

An invention "composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art. *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 418 (2007). "Often, it will be necessary...to look to interrelated teachings of multiple [references]....and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known element in the fashion claimed[.]" *Id.* "[T]his analysis should be made explicit," and it "can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." *Id.* "We must still be careful not to allow hindsight reconstruction of references to reach the claimed invention without any explanation as to how or why the references would be combined to produce the claimed invention." *Innogenetics, N.V. v. Abbott Labs.*, 512 F.3d 1363, 1374 n.3 (Fed. Cir. 2008).

In order to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be an apparent reason why a person of ordinary skill would have combined the prior art elements in the manner claimed. *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991). Second, there must be a reasonable expectation of success. Third, the references when combined, must teach or suggest all the claim limitations. *Id.; Procter & Gamble Co. v. Teva Pharmaceuticals USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009); *see also M.P.E.P. § 2143.*

To sustain a *prima facie* case of obviousness, the Examiner must prevail on all three criteria. A failure on any one precludes a finding of *prima facie* obviousness. As will be articulated hereinbelow, the present rejection cannot be sustained because none of the elements has been satisfied.

According to the M.P.E.P. § 2143 I. A., the rationale to support a conclusion that the claim would have been obvious is that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination yielded nothing more than predictable results to one of ordinary skill in the art. *KSR*, 550 U.S. at 416, 82USPQ2d at 1395; *Sakraida v. AG Pro, Inc.*, 425U.S. 273, 282, 189 USPQ 449, 453 (1976); *Anderson's-Black Rock, Inc. v. Pavement Salvage Co.*, 396 U.S. 57, 62-63, 163 USPQ 673, 675 (1969); *Great Atl. & P. Tea Co. v. Supermarket Equip.Corp.*, 340 U.S. 147, 152, 87 USPQ 303, 306 (1950)."[I]t can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." *KSR*, 550 U.S. at418, 82

USPQ2d at 1396. If any of these findings cannot be made, then this rationale cannot be used to support a conclusion that the claim would have been obvious to one of ordinary skill in the art.

As stated in the M.P.E.P. § 2144.09 VII, a *prima facie* case of obviousness based on structural similarity is rebuttable by proof that the claimed compounds possess unexpectedly advantageous or superior properties. *In re Papesch,* 315 F.2d 381, 137 USPQ43 (CCPA 1963).

C. Reasons to Combine the Elements of the Cited Art Were Not Known

The obviousness rejection is based largely on the Examiner's assertion that it would have been customary for an artisan of ordinary skill to determine the optional weight percent of emulsifier needed to achieve the desired results. The Examiner then states that absent some demonstration of unexpected results from the claimed parameters, the optimization of the weight percent of emulsifier would have been obvious at the time of Applicants' invention.

As discussed during the Examiner Interview, Applicants assert that the instant claims represent identification of a problem not previously recognized by Zhou or Bremer. Specifically, the claimed pharmaceutical emulsion comprising in part 0.4 to 1.0 wt/wt% aprepitant, 13 to 15 wt/wt% egg yolk lecithin, and 9 to 10 wt/wt% soybean oil (e.g., Examples 1, 2, and 6), is pharmaceutically stable for at least the reasons that crystals do not form in the claimed pharmaceutical emulsion after storage for more than, e.g., 4 days at room temperature. As shown in Table 7 on pages 27-28 of the instant specification as filed, the formulations of Examples 1, 2, 3 and 6 were 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, 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 less than 13 wt/wt% egg yolk lecithin (9.95 wt/wt% Lipoid E 80), 0.672 wt/wt% aprepitant and 8.96 wt/wt% soybean oil resulted in an emulsion in which crystals were observed within 4 days post preparation at room temperature.

In the absence of any evidence that a person having ordinary skill in the art (POSA) at the time of filing knew that the aprepitant emulsions taught by Zhou lacked stability, there is no basis for concluding that the present claims would have been obvious over the cited art for at least the reason that there was no motivation to combine the references. Neither Zhou nor Bromer

recognizes the formation of crystals in the emulsions produced as described in each of their references or the effects of 13 to 15 weight percent emulsifier on stability of an emulsion.

D. The Claimed Pharmaceutical Emulsions Possess Unexpected Results and Advantages

Applicants assert that stability (e.g., the lack of crystal formation) of aprepitant emulsions resulting from a formulation comprising *inter alia* 0.4 to 1.0 wt/wt% aprepitant and 13 to 15 wt/wt% egg yolk lecithin demonstrates an unexpected and unpredictable advantage of the claimed pharmaceutical emulsions over the aprepitant formulations of Zhou. Bromer does not cure the defects of Zhou for at least the reason that the formulations of Bromer do not comprise 13 to 15 wt/wt% emulsifier or 0.4 to 1.0 wt/wt% aprepitant. Applicants note that the aprepitant pharmaceutical emulsions generated as described in Examples 1, 2, 3, and 6 have emulsifier weight percentages ranging from 11.7 to 14.3, which fall outside the range of emulsifier weight percent taught by Zhou. None of the emulsions described in Examples 1, 2, 3, and 6 of the instant application showed crystal formation prior to 2 or 3 months storage at room temperature. Examples 4 and 5 contain 9.95 and 2.5 weight percent emulsifier, respectively, and the resultant emulsion of both formed crystals within 4 days of storage at room temperature. Nothing in Zhou or Bremer recognizes the problem of crystal formation in the aprepitant formulations, accordingly, nothing in Zhou or Bremer provides the motivation or guidance for altering the weight percent of emulsifier to arrive at the instantly claimed formulations.

As noted in the Interview Summary by the Examiner mailed August 31, 2016 (hereinafter, "Examiner Interview Summary"), the Examiner requested clarification regarding the differences between the emulsion preparation process described in Example 4 of the instant specification and the emulsion preparation process described in the examples of Zhou. The Examiner questioned whether the unexpected results (e.g., increased stability) was due to a difference in the method of preparing the emulsion. As suggested by the Examiner, Applicants provide with this response a Declaration by Dr. Ottoboni describing the process of emulsion preparation by Zhou and comparing it to the emulsion preparation described in the instant specification. In the Declaration (attached as Exhibit A), Dr. Ottoboni confirms that Example 4 describes an emulsion that was prepared according to the methods taught by Zhou.

During the Examiner Interview, the Examiner also questioned a possible difference in the

method of generating the formulation per Zhou (or Example 4 of the instant application) as compared to Examples 1, 2, 3, and 6 in the instant application for preparing the claimed pharmaceutical emulsions. The Examiner noted that both Example 4 of the instant application and Zhou describe adding ethanol a second time when the oil was added to the mixture of aprepitant and emulsifier. As noted in the Examiner Interview Summary, Dr. Ottoboni directed the Examiner to Example 5 of the instant application. The emulsion of Example 5 shows an initial mixing of aprepitant, egg yolk phospholipid, soybean oil, and oleic acid followed by the addition of ethanol to dissolve the mixture at 70°C. No second step of ethanol addition is performed. As summarized in the Examiner Interview Summary, the emulsion prepared in Example 5 uses a lower weight percent of emulsifier (2.5 wt%). Without being bound by theory, Applicants note that the ratio of emulsifier to aprepitant was lower in both Example 4 and 5 when compared to the other examples. This difference of emulsifier:drug ratio, reflected in the claimed ingredient ranges, may contribute significantly to crystal formation in the aprepitant emulsions.

To summarize the arguments provided above, Applicants submit that the present claims are not obvious over Zhou in view of Bromer for at least the reasons that the Examiner has not identified a reason that would have prompted a POSA in the relevant filed to combine elements and ranges in a way the present claims do and the claimed compositions possess unexpected and unpredictable advantages over the cited art as evidenced by the increased stability of the claimed pharmaceutical emulsions.

Accordingly, Applicants respectfully request withdrawal of the rejections under 35 U.S.C. §103.

V. Double Patenting

Claims 1-21 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-13 and 18-20 of co-pending Application Serial No. 14/859,013.

Applicants herein submit a Terminal Disclaimer in accordance with 37 C.F.R. § 1.321(b) and (c), thereby obviating the above obviousness type double patenting rejections over co-pending Application Serial No. 14/859,013.

VI. Conclusion

No additional fees are believed due with this communication. However, the Commissioner is hereby authorized and requested to charge any deficiency in fees herein to Deposit Account No. 50-5907.

If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to contact the undersigned at (650) 815-7647.

Respectfully submitted,

Date: September 1, 2016

/Susan L. Harlocker/
Susan L. Harlocker
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NOTICE OF ALLOWANCE AND FEE(S) DUE

108547 7590 12/07/2016
McDermott Will & Emery LLP
500 North Capitol Street NW
Washington, DC 20001

EXAMINER
LEVIN, MIRIAM A

ART UNIT	PAPER NUMBER
1613	

DATE MAILED: 12/07/2016

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/083,071	03/28/2016	Thomas B. Ottoboni	092459-0180/8027.US01	9469

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
nonprovisional	SMALL	$480	$0	$0	$480	03/07/2017

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.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

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If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

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III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

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

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/083,071	03/28/2016	Thomas B. Ottoboni	092459-0180/8027.US01	9469

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
nonprovisional	SMALL	$480	$0	$0	$480	03/07/2017

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

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
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3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

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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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❑ Applicant asserting small entity status. See 37 CFR 1.27 — NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
❑ Applicant changing to regular undiscounted fee status. — NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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Washington, DC 20001

EXAMINER
LEVIN, MIRIAM A

ART UNIT	PAPER NUMBER
1613	

DATE MAILED: 12/07/2016

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

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

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

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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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. 15/083,071	Applicant(s) OTTOBONI ET AL.	
	Examiner MIRIAM A. LEVIN	Art Unit 1613	AIA (First Inventor to File) 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 *Request for reconsideration and Declaration filed Sept. 1, 2016*.
   ☐ 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 - 21*. 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 a reply 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 *Search history, BIB*.

/ANNA PAGONAKIS/
Primary Examiner, Art Unit 1628

1. 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

2. Applicant's response filed September 1, 2016 has been received and entered.

Status of Claims

3. Claims Pending: 1 - 21
4. New claims: N/A
5. Amended claims: none
6. Canceled Claims: none
7. Withdrawn claims: 12-21
   a. Rejoinder was requested (telephonic at time of election)
   b. Claims rejoined November 29, 2016

8. Change in Dependency: none
9. Claims under examination: 1 – 21

10. Elected species: N/A

11. Objections/Rejections withdrawn:
    c. 35 USC 103 over Zhou + Bromer vs. cl. 1 - 12
    d. NSDP vs. 14/859013

12. Rejections maintained with revision: none

13. Rejections necessitated by amendment / New Grounds: none

14. Terminal Disclaimers:
    e. Vs. 14/859013
       i. Filed 9/1/2016
       ii. Accepted 9/7/2016

15. There are no rejections against the instant claims.

Election/Restrictions

16. Applicant's election without traverse of Group I, claims 1- 11 in the reply filed on September 1, 2016 is acknowledged.

17. Claims 12 – 21 were withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on September 1, 2016.

18. Claims 1- 11 are directed to an allowable product. Pursuant to the procedures set forth in MPEP § 821.04(B), claims 12 - 21, directed to the process of making or using an allowable product, previously

withdrawn from consideration as a result of a restriction requirement, are hereby rejoined and fully examined for patentability under 37 CFR 1.104.

Because all claims previously withdrawn from consideration under 37 CFR 1.142 have been rejoined, **the restriction requirement as set forth in the Office action mailed on June 3, 2016 is hereby withdrawn**. In view of the withdrawal of the restriction requirement as to the rejoined inventions, applicant(s) are advised that if any claim presented in a continuation or divisional application is anticipated by, or includes all the limitations of, a claim that is allowable in the present application, such claim may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application. Once the restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. See *In re Ziegler*, 443 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

Allowable Subject Matter

19. Claims 1- 21 are allowed.

20. The following is an examiner's statement of reasons for allowance: No reference anticipates the instantly claimed composition and Applicant has demonstrated criticality of the range in regard to the wt. / wt. % of egg yolk lecithin and the ratio of egg yolk lecithin to aprepitant, thereby overcoming any assertion of obviousness the Examiner could make based upon her review of the prior art. While the Examiner treats the comparative data as demonstrating criticality of the range, it is understood that others might regard the same data as showing unexpected results. Either perspective is acceptable and sufficient for the Examiner to find the claims allowable.

21. While other reasons for finding the claims allowable may well exist, the Examiner finds these reasons sufficient.

22. It is noted that in searching copending application 14/859,013 the Examiner also searched for compositions comprising aprepitant or other neurokinin-1 (NK-1) antagonists with a wt. % of any emulsifier in the instantly claimed range, but did not find a reference that taught aprepitant or any other NK-1 antagonist while also teaching a range encompassing or overlapping 13 – 15 wt. % emulsifier, much less one teaching 13 - 15 wt. % egg yolk lecithin.

23. Following are the closest references found by the Examiner. Each is briefly discussed and distinguished. Further support for the allowance may be found in, at least: (a) the experimental data in the specification, (b) the interview summary of August 31, 2016, (c) Applicants' Arguments (Remarks) of September 1, 2016, and (d) the Declaration under 37 CFR 1.132 of Thomas Ottoboni filed September 1, 2016.

24. **Zhou et al.** (CN 102379845 A) (2012) (cited in prior action; cited on IDS; ref. D2 on ISR for PCT/US2016/015992) teaches a formulation for aprepitant comprising 0.05 - 2 wt. % aprepitant and 0.5 - 10 wt. % emulsifier, for example 0.5 g aprepitant and 3 g egg yolk lecithin; the formulation having a total mass of 100 g. (see, cl. 1, 9; Ex. 1, [0019]) The wt. % of the egg yolk lecithin is far too low, as is the ratio of egg yolk lecithin to aprepitant.

25. **Wan et al.** (US 2016/ 0024092 A1) (cited on IDS; ref. D1 on ISR for PCT/US2016/015992) teaches intravenous formulations of neurokinin-1 (NK-1) antagonists comprising 0.88 to 4.84 wt. % emulsifier and 0.2 – 1.0 wt. % of the drug / active, for example, 0.4 - 1.5 wt. % of the NK-1 antagonist and 5.4 wt. % of emulsifier, the emulsifier comprising egg phosphatidylcholine (egg PC), Lipoid E 80S and Lipoid E80; and further comprising sodium oleate, glycerin, ethanol, Miglyol (medium chain triglycerides) and soybean oil (long chain triglycerides). (e.g. [0225], Table 4; Table 15, [0331]; Fig. 3; See also Tables 16 - 20, [[0346] - [0350]; re: composition of Lipoid E80, see [0330], [0347], [0349] (footnote below table 19)). One of the issues faced by Wan et al. was hemolysis upon administration of the composition. Wan et al. note that some formulations with egg PC or Lipoid E80S resulted in clean (little or no hemolysis) formulations. (e.g. [0172]; see also column on hemolysis in tables 15 - 20, [0331] - [0350]) Regardless, Wan et al. fail to teach a composition comprising 13 – 15 wt. % emulsifier, much less one comprising 13 - 15 wt. % egg yolk lecithin, or having a sufficiently high ratio of emulsifier to drug.

26. **Karavas et al.** (WO 2014 / 005606 A1) (cited on IDS; D1 on ISR for PCT /US2015/051050) teach stable injectable pharmaceutical composition of neurokinin 1 receptor antagonist and process for preparation thereof wherein aprepitant and fosaprepitant are exemplary NK-1 receptor antagonists used in the formulations. (e.g. title, Abs.) Karavas et al. teach the composition may comprise 0.1 mg / mL to 350 mg / mL, preferably 1 mg / mL to 150 mg / mL, of a viscosity adjusting agent such as lecithin. (e.g.

p5, pr. 2; note this is the equivalent of 0.001 - 35 w/v % and 0.1 - 15 w/v %. If most of the composition is water, the w/v % is about the same as the w/w %.) Use of lecithin as a viscosity agent is an intended use and is therefore not controlling; the compound will have the same physical and chemical properties regardless of the "role" assigned to it in the reference.

27. The composition further comprises 0.01. – 50 wt. % of a solubilizing or wetting agent (e.g. pr. bridging p. 4 – 5), 0.001 – 50 wt. %, preferably 0.1 – 30 wt. % of the active ingredient (p. 6, last full pr.). It is noted that emulsifiers are sometimes considered a type of wetting agent / solubilizer.

28. As an example of a suitable composition, Karavas et al. teach a composition comprising 14.26 wt. % Fosaprepitant Dimeglumine and 16 wt. %% of PLLA/PEG or Poloxamer 407 copolymers. (e.g. p. 16, Table 9) (Note, the MW of fosaprepitant dimeglumine is 614.41; fosaprepitant is a prodrug of aprepitant, which has a MW of 534.427 g/mole.)

29. However, while Karavas et al. teach that the amount of lecithin may be in the instantly claimed range, and teach examples comprising 16 wt. % solubilizers / wetting agents, Karavas et al. do not provide any specific motivation for the specific selection of lecithin, nor do Karavas et al. appear to recognize that the wt. % of active must be much lower than the wt. % of emulsifier; therefore the relative wt. % of active is much too high compared to the wt. % of solubilizer / wetting agent. Therefore Applicant's demonstration of the criticality of the respective ranges and ratio overcomes any obviousness rejection based on Karavas et al.

30. **Hingorani et al**. (WO 2013/177501 A2) (cited on IDS; D2 on ISR for PCT /US2015/051050) teach aprepitant injectable formulations comprising a co-solvent, surfactant and optionally a secondary co-surfactant. (Title, Abs.) Hingorani et al. teach a composition comprising about 2 or 5 mg / mL aprepitant (about 0.2 or 0.5 wt. %, assuming density of water for composition), 30 vol. % ethanol, about 1.5 w/v % surfactant where the surfactant may be Polysorbate 80, soybean lecithin or egg yolk. (e.g. [0020], [0023], [0024]) As an example, Hingorani et al. teach a composition comprising 130 mg aprepitant plus 1.56 g lipoid E80 in 130 mL which is mostly water. (e.g. p. 16, [0054], [0055] - table 11 and table 12) This works out to about 0.1 wt. % aprepitant and 1.2 wt. % Lipoid E80 (note discussion of references above and instant spec.; Lipoid E80 is largely comprised of egg yolk lecithin), therefore the

ratio of Lipoid E80 to aprepitant is about 12 to 1. While this is much closer to the ratio implicit in the instant claims, it is still too low, as is the wt. % of egg yolk lecithin. The Examiner finds no motivation to increase it to the instantly claimed range or to adjust the weight percentages to provide the ratio implicit in the instant claims. Therefore Applicant's demonstration of criticality of the ranges overcomes any potential assertion of obviousness based on this reference.

31. **Filipcsei et al**. (WO 2011/158053 A1) (cited on IDS and D3 on ISR for PCT/US2015/051050) teach Nanostructured aprepitant compositions, process for the preparation thereof and pharmaceutical compositions containing them. (Title) Filipcsei et al. teach fluidity of an injectable solution may be maintained by the use of a coating such as lecithin (e.g., p. 6, last full pr.), however it is not clear if the coating is to be applied to the syringe, the container or the particles. And, even if it is supposed to be applied to the particles, Filipcsei et al. do not appear to teach a specific amount or ratio. The only other mention of lecithin is in Ex. 5 where "permeability was measured across and [sic] artificial membrane composed of dodecane with 20% soy lecithin." Therefore it is the membrane which contains the soy lecithin, not the pharmaceutical composition. Therefore, even if Filipcsei et al. teach a composition comprising aprepitant and lecithin, they do not appear to teach the required percentage or the implied ratio of lecithin to aprepitant. Applicant's demonstration of criticality of the ranges overcomes any potential assertion of obviousness based upon this reference.

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."

Made of Record

Written Opinion of the International Searching Authority, PCT/US2015/051050 (WO 2016/044784 A1), (document notes date of completion as "see PCT/ISA/210," which is dated 18/12/2015), 6 pages.

Conclusion

Claims 1 - 21 are allowed. No claims are rejected.

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).

/M. A. L./

Examiner, Art Unit 1613

/ANNA PAGONAKIS/

Primary Examiner, Art Unit 1628