Electronic Acknowledgement Receipt

EFS ID:	27977462
Application Number:	15398928
International Application Number:	
Confirmation Number:	6985
Title of Invention:	EMULSION FORMULATIONS OF APREPITANT
First Named Inventor/Applicant Name:	Thomas B. Ottoboni
Customer Number:	108547
Filer:	Susan L. Harlocker/Caroline Benson
Filer Authorized By:	Susan L. Harlocker
Attorney Docket Number:	092459-0203/8027.US02
Receipt Date:	05-JAN-2017
Filing Date:	
Time Stamp:	12:29:45
Application Type:	Utility under 35 USC 111(a)

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RAM confirmation Number	010517INTEFSW00011967505907
Deposit Account	505907
Authorized User	Susan Harlocker

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

37 CFR 1.16 (National application filing, search, and examination fees)

37 CFR 1.17 (Patent application and reexamination processing fees)

37 CFR 1.19 (Document supply fees)

37 CFR 1.20 (Post Issuance fees)

37 CFR 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Application Data Sheet	092459_0203_ADS.pdf	333159 ab277f7fd08f7c62f05fd6d468f9b2ff00f5132d	no	8
Warnings:					
Information:					
This is not an USPTO supplied ADS fillable form					
2		092459_0203_Application.pdf	225059 0262793c5ac424240607fd13a774702908b760ea	yes	34

Multipart Description/PDF files in .zip description

Document Description	Start	End
Specification	1	31
Claims	32	33
Abstract	34	34

Warnings:					
Information:					
3	Drawings-only black and white line drawings	092459_0203_Drawings.pdf	988664 1795d6af28dfa91955000b07d74195106c56124a	no	4
Warnings:					
Information:					
4	Oath or Declaration filed	092459_0203_Oath.pdf	902514 b0233cecf8c5c5c475c6c03c4da03b565ef4a424	no	2
Warnings:					
Information:					

5	Power of Attorney	092459_0203_POATransmittal.pdf	60579 c1e01fbe77d8ff0860e977e3e74d9a99059ef2d0	no	1
Warnings:					
Information:					
6	Power of Attorney	092459_0203_POA.pdf	619647 0ad85ab127312b8b6a6baad51f6518a56c4a4956	no	1
Warnings:					
Information:					
7	Fee Worksheet (SB06)	fee-info.pdf	35113 b775bfdb24c989d8fb55ddf6b78a0ccba8eb1946	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	3164735	

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.

<u>New Applications Under 35 U.S.C. 111</u>
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.

<u>National Stage of an International Application under 35 U.S.C. 371</u>
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.

<u>New International Application Filed with the USPTO as a Receiving Office</u>
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.

WHAT IS CLAIMED IS:

1. An injectable emulsion comprising:

aprepitant;

11 wt/wt% to 15 wt/wt% of an emulsifier;

an oil;

a co-emulsifier which is an alcohol;

a tonicity modifier;

a pH modifier; and

water;

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

2. The emulsion according to claim 1, wherein the ratio of the oil to the aprepitant within the oil phase of the emulsion ranges from about 10:1 to 15:1 (wt/wt%).

3. The emulsion according to claim 1, wherein the ratio of the emulsifier to the aprepitant within the oil phase of the emulsion ranges from about 15:1 to 30:1 (wt/wt%).

4. The emulsion according to claim 1, wherein the ratio of emulsifier to oil ranges from about 1:1 to 3:1 (wt/wt%).

5. The emulsion according to claim 4, wherein the emulsifier is a phospholipid.

6. The emulsion according to claim 1, further comprising dexamethasone sodium phosphate, wherein the dexamethasone sodium phosphate is present in the aqueous phase.

7. The emulsion according to claim 1, wherein the emulsifier is an egg lecithin.

8. The emulsion according to claim 1, further comprising a buffer.

9. The emulsion according to claim 1, wherein the pH modifier is sodium oleate.

10. The emulsion according to claim 8, wherein the buffer is Tris buffer.

11. The emulsion according to claim 1, wherein the oil is soybean oil.

12. The emulsion according to claim 1, wherein the alcohol is ethanol.

13. The emulsion according to claim 12, wherein the ethanol is present at less than 10 wt/wt%.

14. A method for preparing a pharmaceutical emulsion comprising:

combining aprepitant, an emulsifier, and an alcohol with an oil to generate an oil phase;

combining water, a tonicity agent, a pH modifier, and optionally a buffer to generate an aqueous phase;

homogenizing the oil phase with the aqueous phase to generate a coarse emulsion premix;

homogenizing the coarse emulsion premix at a pressure between 10,000 and 30,000 psi using a microfluidizer to generate the pharmaceutical emulsion; and

sterilizing the pharmaceutical emulsion.

15. The method according to claim 14, wherein homogenizing the coarse emulsion premix comprises 4 to 15 passes through the microfluidizer.

16. The method according to claim 14, wherein the sterilizing comprising passing the pharmaceutical emulsion through a filter having a pore size of about 0.2 microns.

17. The method according to claim 14, further comprising adding a solution of dexamethasone sodium phosphate to the fine emulsion prior to sterile filtration.

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/398,928	01/05/2017	Thomas B. Ottoboni	092459-0203/8027.US02	6985

108547 7590 07/19/2018
McDermott Will & Emery LLP
500 North Capitol Street NW
Washington, DISTRICT OF COLUMBIA 20001
UNITED STATES OF AMERICA

EXAMINER
LEVIN, MIRIAM A

ART UNIT	PAPER NUMBER
1613	

NOTIFICATION DATE	DELIVERY MODE
07/19/2018	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

PTOL-90A (Rev. 04/07)

Office Action Summary	Application No. 15/398,928	Applicant(s) Ottoboni et al.	
	Examiner MIRIAM A LEVIN	Art Unit 1613	AIA Status Yes

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

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 2 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 5 January 2017.

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

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

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

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

Disposition of Claims*

5) ☑ Claim(s) 1-17 is/are pending in the application.

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

6) ☐ Claim(s) _____ is/are allowed.

7) ☐ Claim(s) _____ is/are rejected.

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

9) ☑ Claim(s) 1-17 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 _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

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

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

Priority under 35 U.S.C. § 119

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

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

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

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

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

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

Attachment(s)

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

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

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

4) ☐ Other: _____.

Notice of Pre-AIA or AIA Status

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

DETAILED ACTION

Election/Restriction

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

I. Claims 1 - 13, drawn to an injectable emulsion of aprepitant, classified in A61K 9/0019.

II. Claims 14 - 17, drawn to a method of making an emulsion of aprepitant, classified in A61K 9/1

The inventions are independent or distinct, each from the other because:

Inventions I and II are related as process of making and product made. The inventions are distinct if either or both of the following can be shown: (1) that the process as claimed can be used to make another and materially different product or (2) that the product as claimed can be made by another and materially different process (MPEP § 806.05(f)). In the instant case, per the interview of August 31, 2016 with Dr. Ottoboni in parent case 15/083071, aprepitant has both hydrophobic parts and hydrophilic parts, therefore it is best solubilized in emulsifier. As a result, the aprepitant and emulsifier could be added into the aqueous phase rather than into the oil phase. Therefore there are at least two different methods to prepare the instantly claimed product.

Restriction for examination purposes as indicated is proper because all the 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 respective inventions have acquired a separate status in the art in view of their different classification.

The respective inventions require a different field of search (e.g. searching different class/subclasses or electronic resources, or employing different search strategies or search queries).

.

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**.

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.

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.

This application contains claims directed to the following sets of patentably distinct species. **Please select ONE from EACH set of species. Please ensure that the elected species are capable of being used together in a composition or method according to the instant claims, e.g., the HLB of the emulsifier is suitable for preparation of an emulsion comprising a combination of the other elected species**.

- Emulsifiers, e.g. egg yolk lecithin (cl. 7), phosphatidylserine (spec. as filed, pp. 4- 5, [0021] – [0023]), polyoxyethylene sorbitan fatty acid esters or myristoleic acid (e.g., spec., pp. 12 – 13, [0074] – [0077]);
- Oils, e.g. soybean oil (cl. 11), olive oil (e.g. [0012]), or hydrogenated castor oil (e.g. spec as filed, pp. 14 – 15, [0085]; see also p. 13, [0079]);
- Co-emulsifier (alcohol), e.g. ethanol (cl. 12), or hexanol (spec., p. 14, [0087]);
- Tonicity modifier / osmotic agent, e.g. glycerol, sodium chloride or sucrose (spec. p. 6, [0035]; spec. pp. 22 – 31, Examples);

- pH modifier / pH adjusting agent, e.g., sodium oleate (cl. 9), a buffer (spec. [0011], [0031]), or sodium hydroxide or Tris (e.g., spec. p. 6, [0036]), or oleic acid (e.g. spec. pp. 25 – 26, Ex. 5);
- Buffer, e.g. Tris buffer (cl. 10) or phosphate buffered saline (e.g., spec. [0033], [0092] – [0093]).

The species are independent or distinct because different compounds have different chemical structures and therefore different physical and chemical properties. The combination of materials will produce emulsions with different properties and different HLBs, therefore different emulsifiers are required for the different combinations in order to stabilize the respective emulsions.

In addition, these species are not obvious variants of each other based on the current record.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species, or a single grouping of patentably indistinct species, for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, claims 1 and 14 are generic.

There is a search and/or examination burden for the patentably distinct species as set forth above because at least the following reason(s) apply:

The species or groupings of patentably indistinct species have acquired a separate status in the art in view of their different classification.

The species or groupings of patentably indistinct species have acquired a separate status in the art due to their recognized divergent subject matter.

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).

The different compounds have different structures and properties, therefore they are classified in different classes and searches for one species may not produce art reading on other species.

Moreover, attempting to search for all of the possible combinations of compounds will be very time consuming and may produce a vast sea of references that will take hours or days for the Examiner to review. This imposes a significant burden on the Examiner.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species to be examined even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected species or grouping of patentably indistinct species**, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

The election may be made with or without traverse. To preserve 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 election of species 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 on the elected species or grouping of patentably indistinct species.

Should applicant traverse on the ground that the species, or groupings of patentably indistinct species from which election is required, are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing them 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 species 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 species.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141.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).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MIRIAM A LEVIN whose telephone number is (571)270-3471. The examiner can normally be reached on part time basis M-F noon – 10 PM.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an

interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

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

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

/M.A.L/
Examiner, Art Unit 1613

/ERNST V ARNOLD/
Primary Examiner, Art Unit 1613

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF:	EXAMINER: MIRIAM A. LEVIN
THOMAS B. OTTOBONI *ET AL.*	ART UNIT: 1613
APPLICATION NO.: 15/398,928	CONF. NO.: 6985
FILED: January 5, 2017	
FOR: **EMULSION FORMULATIONS OF APREPITANT**	

RESPONSE TO RESTRICTION/ELECTION REQUIREMENT

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

Commissioner:

This communication is in response to the Office Action mailed July 19, 2018 in which it was stated that the claims pending in this application are subject to a restriction/election requirement. Consideration of this response is respectfully requested.

Remarks begin on page 2 of this paper.

REMARKS

I. Restriction Requirement

The Office has requested restriction of the claims to one of the following two groups of claims under 35 U.S.C. §121:

Group I: Claims 1-13, drawn to an injectable emulsion of aprepitant, and

Group II: Claims 14-17, drawn to a method of making an emulsion aprepitant.

In response, Applicant elects claims of Group I, claims 1-13, without traverse. In view of the elections provided herein, Applicant respectfully requests that should the currently elected emulsion claims be found to be allowable, withdrawn method of making claims that include all the limitations of the allowable emulsion claims be considered for rejoinder.

II. Election of Species Requirement

The Office has requested an election of species on which to commence prosecution on the merits. Specifically, the Office has requested an election of (1) emulsifiers, (2) oils, (3) co-emulsifier, (4) tonicity modifier, (5) pH modifier, and (6) buffer.

In response, Applicant elects (1) egg yolk lecithin as the emulsifier, (2) soybean oil as the oil, (3) ethanol as the co-emulsifier, (4) sucrose as the osmotic agent as the tonicity modifier/osmotic agent, (5) sodium oleate as the pH modifier, and (6) TRIS as the buffer.

Claims 1-13 read on the elected species within the claims of Group I.

III. Conclusion

If the Office has questions or believes that a telephonic conference would expedite prosecution of this application, the Office is encouraged to call the undersigned at (650) 815-7399.

No additional fees are believed to be due with this response. However, the

Commissioner is hereby requested to charge any deficiency payment or credit any overpayment to Deposit Account No. 50-5907.

Respectfully submitted,
McDermott Will & Emery

Date: September 19, 2018

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

Correspondence Address:
Customer No. 108547

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/398,928	01/05/2017	Thomas B. Ottoboni	092459-0203/8027.US02	6985

108547 7590 01/18/2019
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
01/18/2019	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

PTOL-90A (Rev. 04/07)

Office Action Summary	Application No. 15/398,928	Applicant(s) Ottoboni et al.	
	Examiner MIRIAM A LEVIN	Art Unit 1613	AIA Status Yes

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

Period for Reply

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

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

Status

1)☑ Responsive to communication(s) filed on September 19, 2018.

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

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

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

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

Disposition of Claims*

5) ☑ Claim(s) 1-17 is/are pending in the application.

5a) Of the above claim(s) 14-17 is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 1-13 is/are rejected.

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

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

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

Application Papers

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

11)☑ The drawing(s) filed on 5 January 2017 is/are: a)☑ accepted or b)☐ objected to by the Examiner.

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

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

Priority under 35 U.S.C. § 119

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

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

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

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

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

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

Attachment(s)

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

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

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

4) ☐ Other: _____.

Notice of Pre-AIA or AIA Status

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

Status of Claims

2. Claims Pending: 1 -17
3. New claims: None
4. Amended claims: None
5. Canceled Claims: None
6. Withdrawn claims: 14 -17
7. Change in Dependency: None

8. Elected group: I (composition)
9. Elected species:
   a. Emulsifier = egg lecithin
   b. Oil = soybean oil
   c. Co-emulsifier = ethanol
   d. Tonicity modifier / osmotic agent = sucrose
   e. pH modifier = sodium oleate
   f. buffer = TRIS

10. Objections/Rejections withdrawn: None

11. Rejections maintained with revision: None

12. New Grounds and/or Rejections necessitated by amendment: None
    g. 35 USC 103 over Zhou (CN 102379845 A)
    h. 35 USC 103 over Zhou + Hargreaves + Sun
    i. 35 USC 103 over Zhou + Karavas + Bromer + Wan

13. Terminal Disclaimers: None

14. Applicant's arguments filed September 19, 2018 have been fully considered. The following rejections constitute the complete set of rejections presently being applied to the instant application.

Election/Restrictions

Applicant's election without traverse of Group 1 and the species indicated above in the reply filed on September 19, 2018 is acknowledged.

Claims 14 – 17 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected Group, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on September 19, 2018.

Claim Rejections - 35 USC § 103

15. In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the statutory basis for the rejection will not be considered a new ground of rejection if the prior art relied upon, and the rationale supporting the rejection, would be the same under either status.

16. 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.

17. 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.

18. Claims 1 – 5, 7 and 11 – 13 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 and ISR). (Note: English translation was attached to the back of the Chinese publication. Citation is made to the English translation, using the page numbers from that document.)

19. 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).

20. Applicant claims: an injectable emulsion comprising:

j. aprepitant;

k. 11 – 15 wt. % emulsifier (elected species egg yolk lecithin);

l. Oil (elected species soybean oil);

m. Co-emulsifier which is an alcohol (elected species ethanol);

n. Tonicity modifier (elected species sucrose);

o. pH modifier (elected species sodium oleate);

p. water;

q. wherein the emulsion has a pH of 7.5 – 9.0.

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

21. Zhou et al. teach aprepitant microemulsion for injection and preparation method thereof. (title)

22. Zhou et al. teach aprepitant is used as an antiemetic to treat delayed CINV. (e.g. [0002], [0003]) CINV is chemotherapy-induced nausea and vomiting.

23. The emulsion comprises, for example:

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

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

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

u. 1 – 10 wt. % co-emulsifier, preferably 7 – 13 wt. % co-emulsifier; alternatively, preferably 2 – 5 wt. %, wherein the co-emulsifier is ethanol;

v. 5 – 20 wt. % of a protective agent (compare vs. tonicity modifier of instant claims), preferably 8 – 13 wt. %, wherein the protective agent may be glycerin, sucrose or glucose;

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

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

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

25. Therefore, Zhou et al. teach or suggest an emulsifier: aprepitant ratio of 20:1 to 1:4, i.e., 10:0.5 to 0.5 to 2.0, based on weight percentages recited above.

26. Zhou et al. teach examples 1 - 6 and 8 with ratios of 1:1 to 13:1 emulsifier: aprepitant. (Ex. 1 - 6, 8)

27. In Ex. 7, Zhou et al. teach 0.2 g aprepitant and 9.8 g of egg yolk phospholipid. ([0032]) First, 0.2 g wt. % of aprepitant is outside the range recited earlier in the document and second, this example provides a 49:1 ratio of emulsifier to aprepitant. **Therefore, Zhou et al. teach that there is some flexibility in the ranges recited earlier in the document.**

28. In regard to the pH, in examples using the egg yolk phospholipid, Zhou et al. teach pHs of 6.8, 7.2 and 8.0. (Ex. 1, 4 – 7)

29. Zhou et al. teach the emulsion may then be lyophilized for later use. (e.g. [0026])

30. Zhou et al. teach that the emulsion may be concentrated into small-volume injection vials. For example, in Ex. 5, 115 mg aprepitant emulsion is placed in a 5 mL vial. The starting emulsion has 2 grams of aprepitant. 2 grams / 0.115 grams = 17.39 aliquots. If each aliquot is 5 mL, that only accounts for 86 mL, which is probably not the entire volume. (See, [0028])

31. In Ex. 6, the emulsion comprises 0.5 g aprepitant, and each 5 mL aliquot comprises 150 mg; or nearly 1/3 of the total. (See, e.g. [0029], [0030]) Clearly this emulsion must have been concentrated prior to being placed in the 5 mL vial.

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

32. The difference between the instant application and Zhou et al. is that Zhou et al. do not expressly teach a weight percent of emulsifier greater than 10 wt. %.

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

33. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to use 11 – 15 wt. % emulsifier, as suggested by Zhou et al., and produce the instant invention.

34. One of ordinary skill in the art would have been motivated to do this because these ranges border on, or are close to, the ranges taught and/or suggested by Zhou et al.

35. Zhou et al. teach 0.5 to 10 wt. % emulsifier, preferably 8 – 10 wt.%, and 0.5 - 2.0 wt. % aprepitant, which provides the teaching, suggestion and /or motivation for a ratio of emulsifier to aprepitant of 20:1 to 1:4, preferably 20:1 to 4:1. Zhou et al. also teach an example using 10 wt. % egg yolk phospholipids and 0.2 wt. % aprepitant, which is an emulsifier: aprepitant ratio of 49:1, thereby teaching that there is flexibility in regard to the ranges recited earlier in the document, i.e. the ranges should be interpreted as preferred or most preferred, but not limiting.

36. With the exception of the emulsifier, the weight percentage of every ingredient, ratio of emulsifier to aprepitant, and pH of the emulsion lie within, overlap or border on the ranges explicitly taught by Zhou et al. The instantly claimed wt. % range of the emulsifier is only slightly above that of Zhou et al. (11 % vs. 10%) and Ex. 7 of Zhou et al. teaches that the ranges are not limiting, therefore slight variations are within the teachings of Zhou.

37. Therefore the claimed ranges for ingredients other than the emulsifier are anticipated or obvious; and the range for the emulsifier is obvious because it borders on the range taught by Zhou et al. and, in the absence of evidence to the contrary, there is no reason to expect that 11 % emulsifier will form a significantly different composition

than would be obtained with 10 % emulsifier. Following are the respective citations to MPEP regarding the various ranges:

38. The range is anticipated. (MPEP 2131.03 (I)(A))

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)

39. The range is obvious (MPEP 2144.05 (I) Overlap of ranges) – including ranges which do not overlap but are close

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) . . .

40. Changes in concentration are routine optimization (MPEP 2144.05 (II)(A)):

2144.05 Obviousness of Ranges [R-5]

II. OPTIMIZATION OF RANGES

A. Optimization Within Prior Art Conditions or Through Routine Experimentation

Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA1955)

41. 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.

42. Claims 1, 7 and 11 – 13 are rejected.

43. In regard to claim 2 and the oil to aprepitant ratio, Zhou teach 5 – 30 wt. % oil, preferably 7 – 15 %, and 0.5 – 2.0 % aprepitant, preferably 1.0 – 1.5 %. The ratio of 10: 1 to 15: 1 for oil to aprepitant falls within that range and is therefore obvious. (MPEP 2144.05 (I))

44. In regard to claims 2 and 3, and the aprepitant and emulsifier being in the oil phase, this will occur due to inherent properties of the compounds and composition:

MPEP 2112.01 (II): "A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990).

45. Claims 2 and 3 are rejected.

46. In regard to claims 4 and 5, and a ratio of 1:1 to 3:1 for emulsifier to oil, Zhou teaches 0.5 – 10 % emulsifier, preferably 8 – 10 %, and 5 – 30 %, preferably 7 – 15 % oil. Therefore the ratio falls within the range and is obvious. (MPEP 2144.05 (I)) Claim 4 is rejected. The other limitations of claim 5 were addressed above. Therefore claim 5 is rejected.

47. 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).

48. 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.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this rejection can be found in the rejection above.

Zhou + Hargreaves + Sun

49. Claim 6 is 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 and ISR) (cited above), as applied to claims 1 – 5, 7 and 11 – 13 above, and in further view of Hargreaves et al. (Development of aprepitant, the first neurokinin-1 receptor antagonist for the prevention of chemotherapy-induced nausea and vomiting, Annals of the New York Academy of Sciences (Ann. N.Y. Acad. Sci.) (2011) 1222: 40-48 (Issue: Pharmaceutical Science to Improve the Human Condition: Prix Galien, 2010), and Sun et al. (Compatibility of intravenous fosaprepitant with intravenous 5-HT3 antagonists and corticosteroids, Cancer Chemother. Pharmacol. (2013) (available on-line July 17, 2013) 72: 509 - 513).

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

50. As discussed above, Zhou et al. teach aprepitant microemulsion for injection and preparation method thereof. Zhou et al. teach aprepitant is used as an antiemetic to treat delayed CINV. (e.g. [0002], [0003])

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

51. The difference between the instant application and Zhou et al. is that Zhou et al. do not expressly teach the composition further comprising dexamethasone sodium phosphate. This deficiency in Zhou et al. is cured by the teachings of Hargreaves et al. and Sun et al.

52. Hargreaves et al. teach development of aprepitant, the first neurokinin-1 receptor antagonist for the prevention of chemotherapy-induced nausea and vomiting (CINV) where "[a]prepitant, in combination with a 5-HT3 receptor antagonist and dexamethasone, optimizes protection against CINV in both the acute and delayed phases compared to the prior standard of care, and is now recommended as the first-line therapy for patients about to be treated with moderately or high emetogenic chemotherapy." (title, abstract, conclusion)

53. Sun et al. teach "Compatibility of intravenous fosaprepitant with intravenous 5-HT3 antagonists and corticosteroids," wherein dexamethasone sodium phosphate is one of two corticosteroids tested, "Fosaprepitant demonstrated compatibility when combined in the same IV infusion bag with common 5-HT3 antagonists and corticosteroids for storage and IV administration . . ." and "[u]se of fosaprepitant in combination with other antiemetics may provide a flexible option for administration of antiemetics to patients receiving moderately or highly emetogenic chemotherapy."(Title, Abs.)

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

54. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to use dexamethasone sodium phosphate in the aprepitant composition to treat CINV, as suggested by Zhou et al., Hargreaves et al., and Sun et al., and produce the instant invention.

55. One of ordinary skill in the art would have been motivated to do this because all three references teach aprepitant to treat CINV (chemotherapy induced nausea and vomiting), Hargreaves et al. teach aprepitant plus dexamethasone and a 5-HT3 antagonist as first-line therapy for CINV, and Sun et al. teach dexamethasone sodium phosphate as a form of the drug that is compatible with aprepitant for IV administration. The combination of references provide strong motivation to use the two drugs in combination to treat CINV, and to use the sodium phosphate salt as a preferred form of dexamethasone. The references also demonstrate a predictable result and /or a reasonable expectation of success.

56. In regard to the dexamethasone being in the aqueous phase, this will occur due to the physical and chemical properties of the drug and composition.

MPEP 2112.01 (II): "A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada,* 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990).

57. Claim 6 is rejected.

58. 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).

59. 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.

Claim Rejections - 35 USC § 103

60. The text of those sections of Title 35, U.S. Code not included in this rejection can be found in the rejection above.

Zhou + Karavas + Bromer + Wan

61. Claims 8 - 10 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 and ISR) (cited above), as applied to claims 1 – 5, 7 and 11 – 13 above, and in further view of Karavas et al. (WO 2014/005606 A1; cited on IDS and ISR), Bromer et al. (US 2007/0071777 A1; cited on IDS) and Wan et al. (US 2016/0024092 A1; cited on IDS and ISR).

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

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

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

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

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

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

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

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

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

ff. (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)

63. The difference between the instant application and Zhou et al. is that while Zhou et al. teach emulsifiers and a desired pH, Zhou et al. do not expressly teach sodium oleate or buffers, such as TRIS. These deficiencies in Zhou et al. are cured by the teachings of Karavas et al., Bromer et al. and Wan et al.

64. Karavas et al. teach stable injectable pharmaceutical compositions of neurokinin 1 receptor antagonist and process for preparation thereof. (Title) The neurokinin 1 receptor antagonist is preferable Aprepitant. (Abs.) The composition comprises 0.01 - 50 wt. % of solubilizing or wetting agents, such as sodium oleate (e.g., p. 4, l. 41 - p. 5, l. 8; p. 6, l. 48 - p. 7, l. 8; p. 9, ll. 28- 37; cl. 9,). The composition has a pH of about 6 to about 8, preferably about 7, which can optionally be obtained using a buffer; the pH adjusters may be acids or acid salts and may have sodium as the counterion / salt. (e.g. p. 5, ll. 19 - 25; p. 6, ll. 41 - 46; p. 7, ll. 30 – 38; p. 9, ll. 20 – 21; p. 9, ll. 39 – 47; cl. 9).

65. 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])

66. Wan et al. teach intravenous formulations of neurokinin-1 antagonists. (Title) Wan et al. teach that TRIS is a suitable buffer for a pH of 7 - 8. (e.g. [0130])

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

67. 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 or TRIS buffer in the composition, as suggested by Zhou et al., Bromer et al., and Wan et al., and produce the instant invention.

68. One of ordinary skill in the art would have been motivated to do this because Zhou et al. teach a desired pH of 6 – 8, but do not recite any particular agent as preferred for adjusting the pH, therefore any suitable compounds may be used. Karavas et al. teach that sodium oleate and buffers may be used in injectable formulations of aprepitant. Bromer et al. teach that sodium oleate may be used a pH adjuster to obtain a pH of 6 - 9, and Wan et al. teach that TRIS may be used to obtain a pH of 7 - 8.

69. In the absence of unexpected results or other evidence to the contrary, the selection of sodium oleate or TRIS buffer is the mere selection of a material suitable for the intended use. (MPEP 2144.07)

70. 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.

71. TRIS buffer is already a buffer solution; therefore it also provides the more stable pH obtained with a buffered solution.

72. As further motivation in regard to the selection of sodium oleate, 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.

73. 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.

74. Claims 8 – 10 are rejected.

75. All of the claims have been rejected.

76. 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).

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

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

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

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

Claims 1-14 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims1 – 21 of U.S. Patent No.9,561,229 B2. Although the claims at issue are not identical, they are not patentably distinct from each other because the instant claims recite an emulsion comprising aprepitant, emulsifier, oil, etc., recite specific species and weight percentages or ratios and the ‘229 recites the same

ingredients and the same percentages and ratios, or obvious variations thereon. (MPEP 2144.05 (I) re: ranges, as cited above) In regard to the method claims, a composition is obvious over a method of using the same composition or an obvious variant thereof.

Claims 1 – 14 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1 – 15 of U.S. Patent No. 9,808,465 B2. Although the claims at issue are not identical, they are not patentably distinct from each other because the instant claims recite an emulsion comprising aprepitant, emulsifier, oil, etc., recite specific species and weight percentages or ratios and the '465 recites the same ingredients and the same percentages and ratios, or obvious variations thereon. (MPEP 2144.05 (I) re: ranges, as cited above) In regard to the method claims, a composition is obvious over a method of using the same composition or an obvious variant thereof.

Claims 1- 14 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-21 of U.S. Patent No. 9,974,742 B2. Although the claims at issue are not identical, they are not patentably distinct from each other because the instant claims recite an emulsion comprising aprepitant, emulsifier, oil, etc., recite specific species and weight percentages or ratios and the '742 recites the same ingredients and the same percentages and ratios, or obvious variations thereon. (MPEP 2144.05 (I) re: ranges, as cited above) In regard to the method claims, a composition is obvious over a method of using the same composition or an obvious variant thereof. It is noted that only claims 22 and 23 of the '742 exclude aprepitant as the active agent.

Claims 1 - 14 rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1 -22 of U.S. Patent No. 9,974,793 B2. Although the claims at issue are not identical, they are not patentably distinct from each other because the

instant claims recite an emulsion comprising aprepitant, emulsifier, oil, etc., recite specific species and weight percentages or ratios and the '793 recites the same ingredients and the same percentages and ratios, or obvious variations thereon. (MPEP 2144.05 (I) re: ranges, as cited above) In regard to the method claims, a composition is obvious over a method of using the same composition or an obvious variant thereof.

Claims 1 - 14 rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1 -21 of U.S. Patent No. 9,974,794 B2. Although the claims at issue are not identical, they are not patentably distinct from each other because the instant claims recite an emulsion comprising aprepitant, emulsifier, oil, etc., recite specific species and weight percentages or ratios and the '794 recites the same ingredients and the same percentages and ratios, or obvious variations thereon. (MPEP 2144.05 (I) re: ranges, as cited above) In regard to the method claims, a composition is obvious over a method of using the same composition or an obvious variant thereof.

Claims 1-14 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 29- 35, 37 – 42, 44 and 45 of copending Application No. 15/965,638 (reference application). Although the claims at issue are not identical, they are not patentably distinct from each other because the instant claims recite an emulsion comprising aprepitant, emulsifier, oil, etc., recite specific species and weight percentages or ratios and the '638 recites the same ingredients and the same percentages and ratios, or obvious variations thereon. (MPEP 2144.05 (I) re: ranges, as cited above) In regard to the method claims, a composition is obvious over a method of using the same composition or an obvious variant thereof. It is noted that only claims 36 and 43 of the '742 exclude aprepitant as the active agent.

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

Conclusion

Claims 1 -13 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

/BRIAN-YONG S KWON/
Supervisory Patent Examiner, Art Unit 1613

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:	Customer Number: 108547
Thomas B. OTTOBONI et al.	Examiner: LEVIN, Miriam A.
Application No.: 15/398,928	Art Unit: 1613
Filed: January 5, 2017	Confirmation No.: 6985
For: EMULSION FORMULATIONS OF APREPITANT	

MS: AMENDMENT
Commissioner For Patents
U.S. Patent & Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

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

Sir:

In response to the Non-Final Office Action mailed January 18, 2019, please consider the above-captioned application in view of the following amendments and remarks.

Amendments to the Claims begin on Page 2.

Remarks begin on Page 4.

AMENDMENTS TO THE CLAIMS

The following Listing of Claims, in which deleted text appears ~~struck through~~ or [[double-bracketed]] and inserted text appears <u>underlined</u>, will replace all prior versions, and listings, of claims in the application.

1. (Currently Amended) An injectable emulsion comprising:
aprepitant;
11 wt/wt% to 15 wt/wt% of an emulsifier;
an oil;
a co-emulsifier which is an alcohol;
a tonicity modifier;
a pH modifier; and
water;
wherein the pH of the emulsion ranges from about 7.5 to 9.0<u>,</u>
<u>wherein the emulsion is physically stable</u>.

2. (Original) The emulsion according to claim 1, wherein the ratio of the oil to the aprepitant within the oil phase of the emulsion ranges from about 10:1 to 15:1 (wt/wt%).

3. (Original) The emulsion according to claim 1, wherein the ratio of the emulsifier to the aprepitant within the oil phase of the emulsion ranges from about 15:1 to 30:1 (wt/wt%).

4. (Original) The emulsion according to claim 1, wherein the ratio of emulsifier to oil ranges from about 1:1 to 3:1 (wt/wt%).

5. (Original) The emulsion according to claim 4, wherein the emulsifier is a phospholipid.

6. (Original) The emulsion according to claim 1, further comprising dexamethasone sodium phosphate, wherein the dexamethasone sodium phosphate is present in the aqueous phase.

7. (Original) The emulsion according to claim 1, wherein the emulsifier is an egg lecithin.

8. (Original) The emulsion according to claim 1, further comprising a buffer.

9. (Original) The emulsion according to claim 1, wherein the pH modifier is sodium oleate.

10. (Original) The emulsion according to claim 8, wherein the buffer is Tris buffer.

11. (Original) The emulsion according to claim 1, wherein the oil is soybean oil.

12. (Original) The emulsion according to claim 1, wherein the alcohol is ethanol.

13. (Original) The emulsion according to claim 12, wherein the ethanol is present at less than 10 wt/wt%.

14. (Withdrawn) A method for preparing a pharmaceutical emulsion comprising:

combining aprepitant, an emulsifier, and an alcohol with an oil to generate an oil phase;

combining water, a tonicity agent, a pH modifier, and optionally a buffer to generate an aqueous phase;

homogenizing the oil phase with the aqueous phase to generate a coarse emulsion premix;

homogenizing the coarse emulsion premix at a pressure between 10,000 and 30,000 psi using a microfluidizer to generate the pharmaceutical emulsion; and

sterilizing the pharmaceutical emulsion.

15. (Withdrawn) The method according to claim 14, wherein homogenizing the coarse emulsion premix comprises 4 to 15 passes through the microfluidizer.

16. (Withdrawn) The method according to claim 14, wherein the sterilizing comprising passing the pharmaceutical emulsion through a filter having a pore size of about 0.2 microns.

17. (Withdrawn) The method according to claim 14, further comprising adding a solution of dexamethasone sodium phosphate to the fine emulsion prior to sterile filtration.

REMARKS

I. Status of the Claims

Claim 1 is amended to indicate that the emulsion is physically stable. Support for the amendments can be found in the application as filed, for example, at paragraph [0108].

Accordingly, there is no issue of new matter.

Upon entry of this paper, claims 1-13 are pending and under examination, claims 14-17 are withdrawn for allegedly being drawn to non-elected subject matter.

II. Claim Rejections – 35 U.S.C. § 103

Claims 1-5, 7, and 11-13 are rejected under 35 U.S.C. §103 as allegedly unpatentable over Zhou et al., CN102379845A, published March 21, 2012 (hereinafter "Zhou").

Claim 6 is rejected under 35 U.S.C. §103 as allegedly unpatentable over Zhou in view of Hargreaves et al. (Annals of the New York Academy of Sciences, 2011, 1222:40-48, hereinafter "Hargreaves") and Sun et al. (Cancer Chemother. Pharmacol., 2013, 72:509-513, hereinafter "Sun").

Claims 8-10 are rejected under 35 U.S.C. §103 as allegedly unpatentable (i.e., obvious) over Zhou in view of Karavas et al. (WO 2014/005606, hereinafter "Karavas"), Bromer et al. (US 2007/0071777, hereinafter "Bromer"), and Wan et al. (US 2016/0024092, hereinafter "Wan")

The present claims are directed to an injectable emulsion which comprises aprepitant, 11 to 15 wt/wt% of an emulsifier, an oil, a co-emulsifier which is an alcohol, a tonicity modifier, a pH modifier and water, wherein the pH of the emulsion ranges from about 7.5 to 9.0, and wherein the emulsion is physically stable.

Zhou is cited by the Examiner as the primary reference for its teaching of the use of aprepitant as an antiemetic to treat delayed chemotherapy-induced nausea and vomiting (CINV) and for teaching an aprepitant microemulsion which comprises, e.g., 0.5 to 2.0 wt%, preferably 1.0 to 1.5 wt% aprepitant, 0.5 to 10 wt%, preferably 8 to 10 wt% emulsifier, wherein the emulsifier is egg yolk phospholipids, 5 to 30 wt%, preferably 7 to 15 wt% oil, wherein the oil is soybean oil, 1 to 10 wt%, preferably 7 to 13 wt%, alternatively preferably 2 to 5 wt% co-emulsifier, wherein the co-emulsifier is ethanol, 5 to 20 wt%, preferably 8 to 13 wt% protective agent, wherein the protective agent may be glycerin, sucrose or glucose, and 60 to 80 wt%, preferably 60-69 wt% water. The pH of the microemulsion is 6.0 to 8.0.

The Office asserts that while Zhou does not expressly teach a weight percent of emulsifier greater than 10 wt%, it would have been obvious to one of ordinary skill in the art at the time of invention to use 11 to 15 wt/wt% emulsifier as presently claimed. In particular, the Office contends that the claimed range of 11 to 15 wt/wt% emulsifier borders on the range taught by Zhou and absent evidence to the contrary, here is no reason to expect that 11% emulsifier would form a significantly different composition than would be obtained with 10% emulsifier. The Office further suggests that the difference in wt% emulsifier between Zhou and the present claims is an obvious variant that is arrived at by routine optimization absent some demonstration of unexpected results from the claimed parameters. In response, Applicant details *inter alia* said unexpected results to show that the claims indeed are not obvious in view of Zhou.

The Claimed Pharmaceutical Emulsions Possess Unexpected Results and Advantages

It is Applicant's position that the claims are patentable over Zhou in part because the composition administered to a subject according to the presently claimed method possesses unexpectedly advantageous or superior properties over any aprepitant emulsion taught or suggested by Zhou. Importantly, the stability (e.g., the lack of crystal formation) of aprepitant emulsions resulting from a formulation comprising 11 to 15 wt/wt% egg yolk lecithin (Lipoid E 80) demonstrates an unexpected and unpredictable advantage of the aprepitant emulsions as recited in the present claims over the aprepitant formulations of Zhou.

The aprepitant emulsions generated as described in Examples 1, 2, 3, and 6 have emulsifier weight percentages ranging from about 11.7 to 14.3 wt/wt%, each of which falls within the claimed range of emulsifier but outside the range of emulsifier weight percentages taught by Zhou. As shown in Table 7 on pages 27-28 of the instant specification as filed, the formulations of Examples 1, 2, 3 and 6 lacked 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. 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.

In contrast, emulsions prepared according to Zhou are not stable, readily forming crystals in a short period of time. For example, the emulsion described in Example 4 was prepared according to compositions and methods of Zhou and comprises less than 11 wt/wt% egg yolk lecithin (9.95 wt/wt% Lipoid E 80). Crystals were observed in the resultant emulsion within 4 days post-preparation at room temperature. Example 5 describes preparation of an aprepitant

emulsion comprising 2.5 weight percent emulsifier. Again, crystals were observed in the emulsion within 4 days post-preparation at room temperature.

There is no basis for concluding that the present claims would have been obvious over Zhou for at least the reason that there was no motivation to modify the emulsions of Zhou. Zhou does not suggest or recognize the problem of crystal formation in aprepitant emulsions. Zhou does not suggest potential effects of emulsifier weight percent on stability of an emulsion. A person having ordinary skill in the art at the time of filing could not know that the aprepitant emulsions taught by Zhou lacked stability or that modifying the emulsions of Zhou to comprise 11 wt/wt% to 15 wt/wt% emulsifier.

MPEP §2144.05 (II)(B) provides: "A particular parameter must first be recognized as a result-effective variable, i.e., a variable which achieves a recognized result, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation. *In re Antonie*, 559 F.2d 618, 195 USPQ 6 (CCPA 1977)" Here, the weight percentage of emulsifier was not recognized as a result effective variable with respect to the stability of the emulsion. <u>Accordingly, the Office's routine optimization of emulsifier weight percentage and hence the obviousness analysis lack foundation</u>.

Therefore, the claimed injectable emulsion is not obvious over the teachings of Zhou.

None of the secondary references cure Zhou's deficiencies. Hargreaves is relied upon for teaching that aprepitant in combination with a 5-HT3 receptor antagonist and dexamethasone can optimize protection against CINV in both acute and delayed phases. Sun is cited for teaching compatibility of intravenous fosaprepitant with intravenous 5-HT3 antagonists and corticosteroids (e.g., dexamethasone) for administration of antiemetics to patients receiving moderately or highly emetogenic chemotherapy. The Office cites Karavas for teaching that the pH adjusters may be acids or acid salts and may have sodium as the counterion/salt, Bromer for teaching an emulsion comprising soybean oil, egg yolk lecithin, glycerol, water and sodium oleate, and describing adjusting the pH of the emulsion to 6.0 to 9.0 using sodium oleate, and Wan for teaching an intravenous formulation of neurokinin-1 antagonists and for teaching that TRIS is a suitable buffer for a pH of 7-8.

For the above reasons, the claims under examination are not obvious over the cited references, each alone or in the combination thereof. Withdrawal of the rejections are respectfully requested.

III. Double Patenting

Claims 1-13 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-21 of US Patent No. 9,561,229, claims 1-15 of US Patent No. 9,808,465, claims 1-21 of US Patent No. 9,974,742, claims 1-22 of U.S. Patent No. 9,974,793, and claims 1-21 of US Patent No. 9,974,794.

Claims 1-13 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 29-35, 37-42, 44, and 45 of co-pending US Application No. 15/965,638.

Applicant herein submits terminal disclaimers to obviate the above obviousness type double patenting rejections. Withdrawal of the rejections are respectfully requested.

IV. Conclusion

In view of the above amendments and remarks, Applicant respectfully requests reconsideration of the rejections and timely allowance of the claims.

No 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 call the undersigned at (650) 815-7399.

Respectfully submitted,

Date: April 15, 2019

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

Correspondence Address:

Customer No. 108547

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

108547 7590 07/31/2019
McDermott Will & Emery LLP
500 North Capitol Street NW
Washington, DC 20001

EXAMINER
LEVIN, MIRIAM A

ART UNIT	PAPER NUMBER
1613	

DATE MAILED: 07/31/2019

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/398,928	01/05/2017	Thomas B. Ottoboni	092459-0203/8027.US02	6985

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	$500	$0.00	$0.00	$500	10/31/2019

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.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

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)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

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.

IMPORTANT REMINDER: Maintenance fees are due in utility patents issuing on applications filed on or after Dec. 12, 1980. It is patentee's responsibility to ensure timely payment of maintenance fees when due. More information is available at www.uspto.gov/PatentMaintenanceFees.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via EFS-Web.

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Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

108547 7590 07/31/2019
McDermott Will & Emery LLP
500 North Capitol Street NW
Washington, DC 20001

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

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I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)

(Signature)

(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/398,928	01/05/2017	Thomas B. Ottoboni	092459-0203/8027.US02	6985

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	$500	$0.00	$0.00	$500	10/31/2019

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 03-09 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

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2_____
3_____

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

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

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

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

4a. Fees submitted: ❑Issue Fee ❑Publication Fee (if required) ❑Advance Order - # of Copies _____

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

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❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29

❑ Applicant asserting small entity status. See 37 CFR 1.27

❑ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
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.
NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/398,928	01/05/2017	Thomas B. Ottoboni	092459-0203/8027.US02	6985

108547 7590 07/31/2019
McDermott Will & Emery LLP
500 North Capitol Street NW
Washington, DC 20001

EXAMINER
LEVIN, MIRIAM A

ART UNIT	PAPER NUMBER
1613	

DATE MAILED: 07/31/2019

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 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

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

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
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. 15/398,928	Applicant(s) Ottoboni et al.	
	Examiner MIRIAM A LEVIN	Art Unit 1613	AIA (FITF) 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 Amendment of April 15, 2019; interview of July 18, 2019.
   ☐ 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 1-17 . As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see **http://www.uspto.gov/patents/init_events/pph/index.jsp** or send an inquiry to **PPHfeedback@uspto.gov.**

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

   Certified copies:

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

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

   * Certified copies not received: _____ .

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

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

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

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

Attachment(s)

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

/M.A.L/ Examiner, Art Unit 1613	/BRIAN-YONG S KWON/ Supervisory Patent Examiner, Art Unit 1613

Continuation of Attachment(s) 7. Other: Search notes, search history, Fax with claim amendments, interview summary from 15/083,071

Notice of Pre-AIA or AIA Status

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

Status of Claims

2. Claims Pending: 1 -17
3. New claims: None
4. Amended claims: claim 1
   a. Cl. 2, 3 and 14 – see Examiner's amendment below
5. Canceled Claims: None
6. Withdrawn claims: 14 -17
   b. Rejoined in this action
7. Change in Dependency:
   c. Ex. Amendment ties cl. 14, and therefore 15 -17, to cl. 1

8. Elected group: I (composition)
9. Elected species:
   d. Emulsifier = egg lecithin
   e. Oil = soybean oil
   f. Co-emulsifier = ethanol
   g. Tonicity modifier / osmotic agent = sucrose
   h. pH modifier = sodium oleate
   i. buffer = TRIS

10. Objections/Rejections withdrawn:
    j. 35 USC 103 over Zhou (CN 102379845 A)
    k. 35 USC 103 over Zhou + Hargreaves + Sun
    l. 35 USC 103 over Zhou + Karavas + Bromer + Wan

11. Rejections maintained with revision: None

12. New Grounds and/or Rejections necessitated by amendment:
    m. 35 USC 112 (a) vs. cl. 2
    n. 35 USC 112 (b) vs. cl. 2, 3

13. Terminal Disclaimers:
    o. TD filed, and accepted, on 4/15/2019:
       i. 15/965,638
       ii. US 9,974,794
       iii. US 9,974,793
       iv. US 9,974,742

v. US 9,808,465
vi. US 9,561,229

14. Allowable claims: 1 and 4 - 13

15. Applicant's arguments filed April 15, 2019 have been fully considered. Rejections not reiterated from previous Office actions are hereby withdrawn. There are no rejections presently being applied to the instant application.

EXAMINER'S AMENDMENT

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in an interview with Wen Li on July 18, 2019.

The application has been amended as indicated below (and per the attached Fax from Wen Li). All other claims (cl. 1, 4 – 13, 15 -17) are per the amendment of April 15, 2019.

2. (Currently Amended) The emulsion according to claim 1, wherein the ratio of the oil to the aprepitant ~~within the oil phase of~~ in the emulsion ranges from about [[10:1]]11:1 to 15:1 (wt/wt%).

3. (Currently Amended) The emulsion according to claim 1, wherein the ratio of the emulsifier to the aprepitant ~~within the oil phase of~~ in the emulsion ranges from about 15:1 to 30:1 (wt/wt%).

14. (Currently Amended) A method for preparing a pharmaceutical emulsion according to claim 1 comprising:

combining the aprepitant, [[an]]the emulsifier, and [[an]] the alcohol with [[an]]the oil to generate an oil phase;
combining water, [[a]]the tonicity agent, [[a]]the pH modifier, and optionally [[a]]the buffer to generate an aqueous phase;
homogenizing the oil phase with the aqueous phase to generate a coarse emulsion premix;
homogenizing the coarse emulsion premix at a pressure between 10,000 and 30,000 psi using a microfluidizer to generate the pharmaceutical emulsion; and
sterilizing the pharmaceutical emulsion.

Reasons for Allowance

Claims 1 -17 are allowed.

The following is an examiner's statement of reasons for allowance: No art, alone or in combination with any other reference, teaches the limitations of instant claim 1.

The closest prior art is Zhou et al. (CN 102379845 A; published March 21, 2012, cited on IDS and ISR, cited in prior action).

The teachings of Zhou et al. were discussed in detail in the prior office action. Of particular relevance, Zhou et al. teaches an emulsion comprising 0.5 – 2.0 wt. % aprepitant, preferably 1.0 – 1.5 wt. %, and 0.5 – 10 % emulsifier, preferably 8 – 10 wt. % emulsifier, where the emulsifier is egg yolk phospholipids. (cl. 1, 5 – 9; [0008] – [0011]; examples)

However, as argued by Applicant, the instantly claimed composition exhibits unexpected results in terms of physical stability, i.e. lack of crystal formation. (Remarks, pp. 5 - 6) Examples 1 – 3 and 6 of the instant specification have emulsifier weight percentages falling within the range of 11 – 15 wt. %, i.e. 11.7 – 14.3 wt. % and lacked crystal formation when the emulsions were stored at room temperature for at least 2 months and, in regard to example 2, for at least 3 months. (Remarks, p. 5; spec., pp. 27 -28) In contrast, Examples 4 and 5, which contain less than11 wt. % egg yolk lecithin, which corresponds to the teachings of Zhou, show crystal formation within 4 days. (e.g., Remarks, p. 5; Spec., pp. 25 -26)

As argued by Applicant, one of skill in the art would not have expected the difference between 9.95 wt. % egg yolk lecithin (Ex. 4) and 11.7 wt. % egg yolk lecithin (Ex. 3) to produce such a difference in physical stability. (Remarks, p. 5; Spec. pp. 23 – 25, 27 - 28) The Examiner agrees.

Further, as argued by Applicant, there is no motivation to modify Zhou to increase the amount of emulsifier above 10 wt. %, nor does Zhou teach the potential effects of the emulsifier on the stability of the emulsion. (Remarks, pp. 5- 6) The Examiner agrees.

Applicant argues that none of the secondary references overcome these deficiencies in Zhou. (Remarks, p. 7) The Examiner agrees.

Therefore, the rejections over Zhou were withdrawn.

In regard to the Double Patenting rejections, Applicant argues that the terminal disclaimer overcomes the rejections. (Remarks, p. 7) The Examiner agrees. The double patenting rejections are withdrawn.

The Examiner further notes that, while the Examples in the instant specification use egg yolk lecithin as the emulsifier, the Examiner has found no reason to believe that egg yolk lecithin would perform differently in this composition when compared to other emulsifiers. Therefore the claims are not limited to egg yolk lecithin as the emulsifier.

Therefore claims 1 – 17 are allowed.

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

Response to Arguments

Applicant's arguments, see Remarks, filed April 16, 2019, with respect to the rejections under 35 USC 103 have been fully considered and are persuasive. The rejections under 35 USC 103 have been withdrawn.

Applicant argues that the instantly claimed composition exhibits unexpected results in terms of physical stability, i.e. lack of crystal formation. (Remarks, p. 5) Applicant refers the Examiner to the examples in the instant specification. (Remarks, pp. 5, 6) Examples 1 – 3 and 6 have emulsifier weight percentages falling within the range of 11 – 15 wt. %, i.e. 11.7 – 14.3 wt. % and lacked crystal formation when the emulsions were stored at room temperature for at least 2 months and, in regard to Example 2, for at least 3 months. (Remarks, p. 5; spec., pp. 27 -28) In contrast, Examples 4 and 5, which contain less than11 wt. % egg yolk lecithin, which

corresponds to the teachings of Zhou, show crystal formation within 4 days. (e.g., Remarks, p. 5; Spec., pp. 25 -26)

Applicant argues that one of skill in the art would not have expected the difference between 9.95 wt. % egg yolk lecithin (Ex. 4) and 11.7 wt. % egg yolk lecithin (Ex. 3) to produce such a difference in physical stability. (Remarks, p. 5; Spec. pp. 23 – 25, 27 - 28) The Examiner agrees.

Applicant further argues there is no motivation to modify Zhou to increase the amount of emulsifier above 10 wt. %, nor does Zhou teach the potential effects of the emulsifier on the stability of the emulsion. (Remarks, pp. 5- 6) The Examiner agrees.

Applicant argues that none of the secondary references overcome these deficiencies in Zhou. (Remarks, p. 7) The Examiner agrees.

Therefore, the rejections over Zhou are withdrawn.

In regard to the Double Patenting rejections, Applicant argues that the terminal disclaimer overcomes the rejections. (Remarks, p. 7) The Examiner agrees. The double patenting rejections are withdrawn.

All of the arguments have been considered. The arguments are persuasive. Therefore the rejections are withdrawn.

Conclusion

Claims 1 – 17 are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MIRIAM A LEVIN whose telephone number is (571)270-3471. The examiner can normally be reached on part time basis Monday – Friday, noon – 10 PM, Eastern Time.

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

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

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

/M.A.L/
Examiner, Art Unit 1613

/BRIAN-YONG S KWON/
Supervisory Patent Examiner, Art Unit 1613