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Honigman Miller Schwartz and Cohn LLP/Ipsen
350 East Michigan Avenue, Suite 300
Kalamazoo, MI 49007

EXAMINER	
SHOMER, ISAAC	

ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
07/14/2017	ELECTRONIC

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

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

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

patents@honigman.com
lzerby@honigman.com
anelson@honigman.com

Office Action Summary	Application No. 15/227,561	Applicant(s) HONG ET AL.	
	Examiner ISAAC SHOMER	Art Unit 1612	AIA (First Inventor to File) Status No

-- 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 *3 August 2016*.

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

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

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; 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) *1-20* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-20* 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 _____ 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: _____.

DETAILED ACTION

Notice of Pre-AIA or AIA Status

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

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.

Claim Interpretation

The instant claims recite the term “lipid matrix.” As best understood by the examiner, the term “lipid matrix” is understood to refer to various lipidic structures. These structures include, but are not limited to, liposomal and/or lipid vesicle structures comprising a phospholipid bilayer and an aqueous interior core. See e.g. page 96, paragraph 0242 of the instant specification, which refers to a liposome as a matrix. Both a liposome and a lipid vesicle are understood to comprise an aqueous core surrounded by at least one lipid bilayer.

Non-Statutory 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 1-20 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-35 of U.S. Patent No. 8,147,867 in view of Kirpotin (US Patent 6,110,491).

The instant claims are drawn to a lipid matrix composition comprising phospholipids, sucrose octasulfate, and irinotecan, at a specific size of 110 nm. The claims require a specific amount of 500 mg irinotecan per mmol of lipids.

Conflicting claim 1 is drawn to a liposomal irinotecan composition that also includes sucrose octasulfate. The claims recite about 550 mg of irinotecan per mmol of neutral phospholipids.

The conflicting claims do not recite the required liposome size.

Kirpotin is drawn to liposomes comprising an encapsulated compound, as of Kirpotin, title and abstract. Liposomes of Kirpotin are most preferably sized from about 0.03 to 0.2 microns (30 nm to 200 nm), as of Kirpotin, column 1, lines 1-12.

It would have been prima facie obvious for one of ordinary skill in the art to have sized the liposomes of the conflicting claims in the range taught by Kirpotin. The

liposomes of the conflicting claims are used for drug delivery of irinotecan with sucrose octasulfate. However, the conflicting claims are silent as to the liposome size. As Kirpotin teaches a size range of 30 nm to 200 nm as a useful size range for liposomes that are used to delivery drugs, the skilled artisan would have been motivated to have sized the liposomes of the conflicting claims in the size range taught by Kirpotin. This size range overlaps with the claimed size range, resulting in a prima facie case of obviousness-type non-statutory double patenting.

The instant and conflicting claims also differ because the conflicting claims recite an amount of irinotecan of about 550 mg per neutral phospholipid, as of conflicting claim 24, whereas the instant claims recite 500 mg of irinotecan per mmol of phospholipids. Nevertheless, the skilled artisan would have been motivated to have optimized the amount of irinotecan to have been delivered in order to most effectively have treated the patient to whom the liposomal composition was to have been administered with a reasonable expectation of success. As such, this small difference in the amount of irinotecan fails to overcome the case of obviousness-type non-statutory double patenting.

Claims 1-20 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-17 of U.S. Patent No. 8,329,213 in view of Kirpotin (US Patent 6,110,491).

The instant claims are drawn to a lipid matrix composition comprising phospholipids, sucrose octasulfate, and irinotecan, at a specific size of 110 nm. The claims require a specific amount of 500 mg irinotecan per mmol of lipids.

The conflicting claims are drawn to a liposome comprising irinotecan and sucrose octasulfate, as of conflicting claim 11. Liposomes are understood to comprise phospholipids.

The conflicting claims do not recite the required liposome size.

Kirpotin is drawn to liposomes comprising an encapsulated compound, as of Kirpotin, title and abstract. Liposomes of Kirpotin are most preferably sized from about 0.03 to 0.2 microns (30 nm to 200 nm), as of Kirpotin, column 1, lines 1-12.

It would have been prima facie obvious for one of ordinary skill in the art to have sized the liposomes of the conflicting claims in the range taught by Kirpotin. The liposomes of the conflicting claims are used for drug delivery of irinotecan with sucrose octasulfate. However, the conflicting claims are silent as to the liposome size. As Kirpotin teaches a size range of 30 nm to 200 nm as a useful size range for liposomes that are used to delivery drugs, the skilled artisan would have been motivated to have sized the liposomes of the conflicting claims in the size range taught by Kirpotin. This size range overlaps with the claimed size range, resulting in a prima facie case of obviousness-type non-statutory double patenting.

The instant and conflicting claims differ because the instant claims recite 500 mg of irinotecan per mmol of total lipid matrix phospholipids. In contrast, conflicting claim 12 recites a ratio of 0.05 to 0.3 mmol irinotecan to mmol phospholipid. Given an irinotecan

molecular weight of about 586 mg/mmol, this is about 29 mg irinotecan to 176 mg irinotecan per mmol of lipids. Nevertheless, the skilled artisan would have been motivated to have optimized the amount of irinotecan to have been delivered in order to most effectively have treated the patient to whom the liposomal composition was to have been administered with a reasonable expectation of success. As such, this small difference in the amount of irinotecan fails to overcome the case of obviousness-type non-statutory double patenting.

Claims 1-20 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-17 of U.S. Patent No. 8,703,181 in view of Kirpotin (US Patent 6,110,491).

The instant claims are drawn to a lipid matrix composition comprising phospholipids, sucrose octasulfate, and irinotecan, at a specific size of 110 nm. The claims require a specific amount of 500 mg irinotecan per mmol of lipids.

The conflicting claims are drawn to a method of delivering an antineoplastic agent, including irinotecan, as of conflicting claim 11. This method involves using a liposome comprising irinotecan and sucrose octasulfate. As such, the composition used in the method of the conflicting claims appears to include the components used in the instantly claimed liposome.

The conflicting claims do not recite the required liposome size.

Kirpotin is drawn to liposomes comprising an encapsulated compound, as of Kirpotin, title and abstract. Liposomes of Kirpotin are most preferably sized from about 0.03 to 0.2 microns (30 nm to 200 nm), as of Kirpotin, column 1, lines 1-12.

It would have been prima facie obvious for one of ordinary skill in the art to have sized the liposomes of the conflicting claims in the range taught by Kirpotin. The liposomes of the conflicting claims are used for drug delivery of irinotecan with sucrose octasulfate. However, the conflicting claims are silent as to the liposome size. As Kirpotin teaches a size range of 30 nm to 200 nm as a useful size range for liposomes that are used to delivery drugs, the skilled artisan would have been motivated to have sized the liposomes of the conflicting claims in the size range taught by Kirpotin. This size range overlaps with the claimed size range, resulting in a prima facie case of obviousness-type non-statutory double patenting.

The instant and conflicting claims differ because the instant claims recite 500 mg of irinotecan per mmol of total lipid matrix phospholipids. In contrast, conflicting claim 12 recites a ratio of 0.05 to 0.3 mmol irinotecan to mmol phospholipid. Given an irinotecan molecular weight of about 586 mg/mmol, this is about 29 mg irinotecan to 176 mg irinotecan per mmol of lipids. Nevertheless, the skilled artisan would have been motivated to have optimized the amount of irinotecan to have been delivered in order to most effectively have treated the patient to whom the liposomal composition was to have been administered with a reasonable expectation of success. As such, this small difference in the amount of irinotecan fails to overcome the case of obviousness-type non-statutory double patenting.

Claims 1-20 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-14 of U.S. Patent No. 8,992,970 in view of Kirpotin (US Patent 6,110,491).

The instant claims are drawn to a lipid matrix composition comprising phospholipids, sucrose octasulfate, and irinotecan, at a specific size of 110 nm. The claims require a specific amount of 500 mg irinotecan per mmol of lipids.

The conflicting claims are drawn to liposomes comprising phospholipids, irinotecan, sucrose octasulfate, and a substituted ammonium compound used for loading the irinotecan.

The conflicting claims do not recite the required liposome size.

Kirpotin is drawn to liposomes comprising an encapsulated compound, as of Kirpotin, title and abstract. Liposomes of Kirpotin are most preferably sized from about 0.03 to 0.2 microns (30 nm to 200 nm), as of Kirpotin, column 1, lines 1-12.

It would have been prima facie obvious for one of ordinary skill in the art to have sized the liposomes of the conflicting claims in the range taught by Kirpotin. The liposomes of the conflicting claims are used for drug delivery of irinotecan with sucrose octasulfate. However, the conflicting claims are silent as to the liposome size. As Kirpotin teaches a size range of 30 nm to 200 nm as a useful size range for liposomes that are used to delivery drugs, the skilled artisan would have been motivated to have sized the liposomes of the conflicting claims in the size range taught by Kirpotin. This

size range overlaps with the claimed size range, resulting in a prima facie case of obviousness-type non-statutory double patenting.

The instant claims require 500 mg of irinotecan per mmol of lipids. Conflicting claim 9 recites a molar ratio of irinotecan to lipids of at least 1.0. Given a molecular weight of irinotecan of about 586 mg/mmol, this is an amount of about 586 mg of irinotecan per mmol of lipids. While this amount slightly exceeds the claimed concentration of irinotecan, the skilled artisan would have been motivated to have optimized the amount of irinotecan to have been delivered in order to most effectively have treated the patient to whom the liposomal composition was to have been administered with a reasonable expectation of success. As such, this small difference in the amount of irinotecan fails to overcome the case of obviousness-type non-statutory double patenting.

Claims 1-20 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-22 of U.S. Patent No. 8,658,203 in view of Kirpotin (US Patent 6,110,491).

The instant claims are drawn to a lipid matrix composition comprising phospholipids, sucrose octasulfate, and irinotecan, at a specific size of 110 nm. The claims require a specific amount of 500 mg irinotecan per mmol of lipids.

The conflicting claims are drawn to a method of administration of a composition for treating a brain tumor. This composition used in this method is a liposomal composition comprising phospholipids, irinotecan and sucrose octasulfate. The amount

of irinotecan is 500 grams per mole of phospholipid, as of conflicting claim 3, which is equivalent to 500 mg per mmol of phospholipid.

The conflicting claims do not recite the required liposome size.

Kirpotin is drawn to liposomes comprising an encapsulated compound, as of Kirpotin, title and abstract. Liposomes of Kirpotin are most preferably sized from about 0.03 to 0.2 microns (30 nm to 200 nm), as of Kirpotin, column 1, lines 1-12.

It would have been prima facie obvious for one of ordinary skill in the art to have sized the liposomes of the conflicting claims in the range taught by Kirpotin. The liposomes of the conflicting claims are used for drug delivery of irinotecan with sucrose octasulfate. However, the conflicting claims are silent as to the liposome size. As Kirpotin teaches a size range of 30 nm to 200 nm as a useful size range for liposomes that are used to delivery drugs, the skilled artisan would have been motivated to have sized the liposomes of the conflicting claims in the size range taught by Kirpotin. This size range overlaps with the claimed size range, resulting in a prima facie case of obviousness-type non-statutory double patenting.

Claims 1-20 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-30 of U.S. Patent No. 9,492,442.

The instant claims are drawn to a lipid matrix composition comprising phospholipids, sucrose octasulfate, and irinotecan, at a specific size of 110 nm. The claims require a specific amount of 500 mg irinotecan per mmol of lipids.

The conflicting claims are drawn to a method for treating pancreatic cancer. The method of the conflicting claims utilizes a liposome comprising irinotecan sucrose octasulfate, as well as phospholipids and cholesterol, as of conflicting claim 3. Liposome size is from 80 nm to 140 nm, as of conflicting claim 1.

The instant and conflicting claims differ because the instant claims require 500 mg of irinotecan per mmol of total lipids. While the conflicting claims recite concentration, it is in different units of mg per m^2 (e.g. as of conflicting claim 1). Nevertheless, the skilled artisan would have been motivated to have optimized the amount of irinotecan to have been delivered in order to most effectively have treated the patient to whom the liposomal composition was to have been administered with a reasonable expectation of success.

Note Regarding Apparent Common Assignment: The examiner notes that while there are no common inventors between the instant application and the ‘442 patent, there does appear to be a common assignment. Both the instant application and the '442 patent appear to be assigned to Ipsen Biopharm Ltd. (Although the printing of the '442 patent discloses that the assignee is Merrimack Pharmaceuticals, the assignment appears to have been changed to Ipsen Biopharm Ltd., as of the application data sheet submitted on 05/16/2017 in the file wrapper of application 14/851,111, which is the application that became the '442 patent).

Claims 1-20 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-5, 13, and 24-36 of

copending Application No. 14/632,422 (reference application – currently allowed but not yet issued). Although the claims at issue are not identical, they are not patentably distinct from each other because of the following reasons.

The instant claims are drawn to a lipid matrix composition comprising phospholipids, sucrose octasulfate, and irinotecan, at a specific size of 110 nm. The claims require a specific amount of 500 mg irinotecan per mmol of lipids.

The copending claims are drawn to a method of making a liposomal composition of an antineoplastic agent, wherein said antineoplastic agent is irinotecan, as of copending claim 1. Said composition made by the method of the copending claims is a liposomal composition comprising sucrose octasulfate and irinotecan. Liposomes are sized from about 110 nm to about 120 nm, as of copending claim 24. Amounts of irinotecan range from about 150 to about 550 mg per mmol of liposome lipid, as of copending claim 24.

The instant and copending claims differ because the instant claims are drawn to a composition, whereas the copending claims are drawn to a method of making the composition. Nevertheless, the method of the copending claims would have made a composition that includes all of the features of the instantly claimed composition, resulting in a prima facie case of non-statutory double patenting.

The instant and copending claims differ because the instant claims recite specific values of size and irinotecan concentration, whereas the copending claims recite a range. Nevertheless, the range of the copending claims overlaps with the values

required by the instant claims, resulting in a prima facie case of obviousness-type non-statutory double patenting.

Claims 1-20 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-10 and 12-21 of copending Application No. 14/879,302 (reference application – currently allowed but not yet issued). Although the claims at issue are not identical, they are not patentably distinct from each other because of the following reasons.

The instant claims are drawn to a lipid matrix composition comprising phospholipids, sucrose octasulfate, and irinotecan, at a specific size of 110 nm. The claims require a specific amount of 500 mg irinotecan per mmol of lipids.

The copending claims are drawn to a method of treatment comprising parenteral administration of a liposomal irinotecan composition comprising irinotecan sucrose octasulfate, as of copending claim 1. The amount of irinotecan ranges from 150 mg to 500 mg per mmol liposome phospholipids, as of copending claim 1. Liposome size can be about 110 nm to 120 nm, as of copending claim 12(h).

The instant and copending claims differ because the instant claims are drawn to a composition, whereas the copending claims are drawn to a method of using the composition. Nevertheless, the method of the copending claims utilizes a composition that includes all of the features of the instantly claimed composition, resulting in a prima facie case of non-statutory double patenting.

The instant and copending claims differ because the instant claims recite specific values of size and irinotecan concentration, whereas the copending claims recite a range. Nevertheless, the range of the copending claims overlaps with the values required by the instant claims, resulting in a prima facie case of obviousness-type non-statutory double patenting.

Claims 1-20 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1 and 45-63 of copending Application No. 14/965,140 (reference application – currently allowed but not yet issued). Although the claims at issue are not identical, they are not patentably distinct from each other because of the following reasons.

The instant claims are drawn to a lipid matrix composition comprising phospholipids, sucrose octasulfate, and irinotecan, at a specific size of 110 nm. The claims require a specific amount of 500 mg irinotecan per mmol of lipids.

Copending claim 1 is drawn to an irinotecan sucrose octasulfate in lipid vesicles. These lipid vesicles may include phospholipids, as of copending claim 45, and the amount of irinotecan is 500 mg per mmol of phospholipids, as of copending claim 45. Liposomes have a size of about 110 nm, as of copending claim 63.

The instant and copending claims differ because no single copending claim recites all of the features of the instant claims. For example, copending claim 63 recites the required liposome size but also recites a concentration range of irinotecan that overlaps with but does not read on the claimed size requirements. As such, there is no

case of statutory double patenting. Nevertheless, the copending claims recite all of the subject matter required by the instant claims in separate copending claims, resulting in a prima facie case of non-statutory double patenting.

Claims 1-20 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-3, 5-11, and 17-23 of copending Application No. 14/966,458 (reference application – currently allowed but not yet issued) in view of Kirpotin (US Patent 6,110,491).

The instant claims are drawn to a lipid matrix composition comprising phospholipids, sucrose octasulfate, and irinotecan, at a specific size of 110 nm. The claims require a specific amount of 500 mg irinotecan per mmol of lipids.

Copending claim 1 is drawn to a liposome comprising irinotecan and a sulfated sugar in a lipid vesicle. Said sulfate sugar may be sucrose octasulfate, as of copending claim 6.

The copending claims are silent as to liposome size.

Kirpotin is drawn to liposomes comprising an encapsulated compound, as of Kirpotin, title and abstract. Liposomes of Kirpotin are most preferably sized from about 0.03 to 0.2 microns (30 nm to 200 nm), as of Kirpotin, column 1, lines 1-12.

It would have been prima facie obvious for one of ordinary skill in the art to have sized the liposomes of the conflicting claims in the range taught by Kirpotin. The liposomes of the conflicting claims are used for drug delivery of irinotecan with sucrose octasulfate. However, the conflicting claims are silent as to the liposome size. As

Kirpotin teaches a size range of 30 nm to 200 nm as a useful size range for liposomes that are used to delivery drugs, the skilled artisan would have been motivated to have sized the liposomes of the conflicting claims in the size range taught by Kirpotin. This size range overlaps with the claimed size range, resulting in a prima facie case of obviousness-type non-statutory double patenting.

The copending claims are silent as to the amount of irinotecan in the composition. Nevertheless, the copending claims recite that irinotecan is present. As such, the skilled artisan would have been motivated to have optimized the concentration of irinotecan, with respect to that of liposome lipids, in order to have predictably optimized the dose of irinotecan to have predictably improved treatment of a patient with a reasonable expectation of success.

Claims 1-20 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-20 of copending Application No. 15/227,631 (reference application). Although the claims at issue are not identical, they are not patentably distinct from each other because of the following reasons.

The instant claims are drawn to a lipid matrix composition comprising phospholipids, sucrose octasulfate, and irinotecan, at a specific size of 110 nm. The claims require a specific amount of 500 mg irinotecan per mmol of lipids.

Copending claim 1 is drawn to a matrix comprising phospholipids, sucrose octasulfate, and irinotecan. Said matrix is sized at a size of 110 nm and has 500-550 mg of irinotecan per mmol of phospholipids.

The instant and copending claims differ because the copending claims recite an amount of 500-550 mg of irinotecan per mmol of phospholipids, whereas the instant claims are drawn to an amount of 500 mg of irinotecan per total matrix phospholipids. Nevertheless, the subject matter of the copending claims overlaps with that of the instant claims, resulting in a prima facie case of non-statutory double patenting.

Claims 1-20 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claim 1 of copending Application No. 15/296,536 (reference application – currently allowed but not yet issued). Although the claims at issue are not identical, they are not patentably distinct from each other because of the following reasons.

The instant claims are drawn to a lipid matrix composition comprising phospholipids, sucrose octasulfate, and irinotecan, at a specific size of 110 nm. The claims require a specific amount of 500 mg irinotecan per mmol of lipids.

Copending claim 1 is drawn to an irinotecan sucrose octasulfate liposome. Said liposome comprises irinotecan, sucrose octasulfate, and phospholipids among other lipids. Said liposome is sized from 95-110 nm, and has 500-550 mg of irinotecan per total liposome phospholipids.

The instant and copending claims differ because the copending claims recite an amount of 500-550 mg of irinotecan per mmol of phospholipids, whereas the instant claims are drawn to an amount of 500 mg of irinotecan per total matrix phospholipids. Nevertheless, the subject matter of the copending claims overlaps with that of the instant claims, resulting in a prima facie case of non-statutory double patenting.

Claims 1-20 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-24 of copending Application No. 15/241,128 (reference application – currently allowed but not yet issued) in view of Kirpotin (US Patent 6,110,491).

The instant claims are drawn to a lipid matrix composition comprising phospholipids, sucrose octasulfate, and irinotecan, at a specific size of 110 nm. The claims require a specific amount of 500 mg irinotecan per mmol of lipids.

Copending claim 1 is drawn to a method of treating a type of cancer comprising providing an irinotecan liposome. Copending claim 24 recites that the irinotecan liposome comprises precipitated sucrose octasulfate.

Copending claim 1 is silent as to liposome size.

Kirpotin is drawn to liposomes comprising an encapsulated compound, as of Kirpotin, title and abstract. Liposomes of Kirpotin are most preferably sized from about 0.03 to 0.2 microns (30 nm to 200 nm), as of Kirpotin, column 1, lines 1-12.

It would have been prima facie obvious for one of ordinary skill in the art to have sized the liposomes of the conflicting claims in the range taught by Kirpotin. The

liposomes of the conflicting claims are used for drug delivery of irinotecan with sucrose octasulfate. However, the conflicting claims are silent as to the liposome size. As Kirpotin teaches a size range of 30 nm to 200 nm as a useful size range for liposomes that are used to delivery drugs, the skilled artisan would have been motivated to have sized the liposomes of the conflicting claims in the size range taught by Kirpotin. This size range overlaps with the claimed size range, resulting in a prima facie case of obviousness-type non-statutory double patenting.

The copending claims are silent as to the amount of irinotecan in the composition. Nevertheless, the copending claims recite that irinotecan is present. As such, the skilled artisan would have been motivated to have optimized the concentration of irinotecan, with respect to that of liposome lipids, in order to have predictably optimized the dose of irinotecan to have predictably improved treatment of a patient with a reasonable expectation of success.

Note Regarding Common Assignment: The instant and copending applications do not appear to have common inventors. However, the instant and copending applications do appear to be commonly assigned to Ipsen Biopharm Ltd. As such, the double patenting rejection is understood to be proper for the reasons set forth above as well as in view of the fact that the instant and copending applications are commonly assigned.

Claims 1-20 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 2 and 4-22 of copending Application No. 15/241,106 (reference application) in view of Kirpotin (US Patent 6,110,491).

The instant claims are drawn to a lipid matrix composition comprising phospholipids, sucrose octasulfate, and irinotecan, at a specific size of 110 nm. The claims require a specific amount of 500 mg irinotecan per mmol of lipids.

Copending claim 19(a) is drawn to a method of treating cancer comprising administering liposomal irinotecan. Copending claim 20(a) recites that the irinotecan liposome comprise sucrose octasulfate and DSPC, which is a phospholipid.

The copending claims are silent as to liposome size.

Kirpotin is drawn to liposomes comprising an encapsulated compound, as of Kirpotin, title and abstract. Liposomes of Kirpotin are most preferably sized from about 0.03 to 0.2 microns (30 nm to 200 nm), as of Kirpotin, column 1, lines 1-12.

It would have been prima facie obvious for one of ordinary skill in the art to have sized the liposomes of the conflicting claims in the range taught by Kirpotin. The liposomes of the conflicting claims are used for drug delivery of irinotecan with sucrose octasulfate. However, the conflicting claims are silent as to the liposome size. As Kirpotin teaches a size range of 30 nm to 200 nm as a useful size range for liposomes that are used to delivery drugs, the skilled artisan would have been motivated to have sized the liposomes of the conflicting claims in the size range taught by Kirpotin. This

size range overlaps with the claimed size range, resulting in a prima facie case of obviousness-type non-statutory double patenting.

The copending claims are silent as to the amount of irinotecan in the composition. Nevertheless, the copending claims recite that irinotecan is present. As such, the skilled artisan would have been motivated to have optimized the concentration of irinotecan, with respect to that of liposome lipids, in order to have predictably optimized the dose of irinotecan to have predictably improved treatment of a patient with a reasonable expectation of success.

Note Regarding Common Assignment: The instant and copending applications do not appear to have common inventors. However, the instant and copending applications do appear to be commonly assigned to Ipsen Biopharm Ltd. As such, the double patenting rejection is understood to be proper for the reasons set forth above as well as in view of the fact that the instant and copending applications are commonly assigned.

Cited Prior Art

As relevant prior art, the examiner cites Chou et al. (Journal of Bioscience and Bioengineering, Vol. 95, No. 4, 2003, pages 405-408). Chou et al. (hereafter referred to as Chou) is drawn to liposomal irinotecan prepared by pH gradient loading, as of Chou, page 405, title and abstract. Nevertheless, Chou differs from the claimed invention because Chou does not teach sucrose octasulfate. Also, the amount of drug taught by Chou is 0.254 mg drug per mg lipid, as of Chou, page 407, right column, last full

paragraph. Even assuming a molecular weight of phospholipid of about 790 grams per mole (which is the molecular weight of distearoyl phosphatidylcholine), this is a concentration of

$$\frac{0.254\ mg\ irinotecan}{1\ mg\ lipid} \times \frac{790\ mg\ lipid}{1\ mmol\ lipid} = 200\ \frac{mg\ irinotean}{mmol\ lipid}$$

This amount is still less than the lower limit of 500 mg irinotecan per mmol phospholipid. As such, the skilled artisan would have understood that the inclusion of sucrose octasulfate loads over twice the amount of irinotecan that would have been loaded in a liposome that lacks sucrose octasulfate.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ISAAC SHOMER whose telephone number is (571)270-7671. The examiner can normally be reached on 8:00 AM - 5:00 PM Monday-Friday.

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, Frederick F. Krass can be reached on (571)272-0580. 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.

/ISAAC SHOMER/
Primary Examiner, Art Unit 1612

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/227,561	08/03/2016	Keelung Hong	263266-411993	7226

153749 7590 04/26/2018

McNeill Baur PLLC/Ipsen
Ipsen Bioscience, Inc.
125 Cambridge Park Drive
Suite 301
Cambridge, MASSACHUSETTS 02140
UNITED STATES OF AMERICA

EXAMINER
SHOMER, ISAAC

ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
04/26/2018	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):

docketing@mcneillbaur.com
eofficeaction@appcoll.com
patents.us@ipsen.com

Office Action Summary	Application No. 15/227,561	Applicant(s) Hong et al.	
	Examiner ISAAC SHOMER	Art Unit 1612	AIA Status No

-- 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 07 March 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) 1-20 is/are pending in the application.

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

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 1-20 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 _____ 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: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after allowance or after an Office action under *Ex Parte Quayle*, 25 USPQ 74, 453 O.G. 213 (Comm'r Pat. 1935). Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, prosecution in this application has been reopened pursuant to 37 CFR 1.114.

Applicant's submission filed on 7 March 2018 has been entered, and the arguments presented therein have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

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

Claim Interpretation

The instant claims recite the term “lipid matrix.” As best understood by the examiner, the term “lipid matrix” is understood to refer to various lipidic structures. These structures include, but are not limited to, liposomal and/or lipid vesicle structures comprising a phospholipid bilayer and an aqueous interior core. See e.g. page 96, paragraph 0242 of the instant specification, which refers to a liposome as a matrix. Both

a liposome and a lipid vesicle are understood to comprise an aqueous core surrounded by at least one lipid bilayer.

Statutory Double Patenting (Provisional)

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process... may obtain a patent therefor..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the claims that are directed to the same invention so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 1-20 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-20 of copending Application No. 15/896,389 (reference application). This is a provisional statutory double patenting rejection since the claims directed to the same invention have not in fact been patented.

Non-Statutory Double Patenting (Provisional)

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 1-20 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-20 of copending Application No. 15/896,436 (reference application). Although the claims at issue are not identical, they are not patentably distinct from each other because of the following reasons:

The instant claims are drawn to a pharmaceutical composition comprising irinotecan and sucrose octasulfate in a lipid matrix (i.e. liposome) sized at approximately 110 nm. The composition includes 500 mg of irinotecan base per mmol of phospholipids.

The copending claims are drawn to a pharmaceutical composition comprising irinotecan and sucrose octasulfate in a lipid matrix (i.e. liposome) sized at approximately 110 nm. The composition includes 500-550 mg of irinotecan base per mmol of phospholipids.

The instant claims and the copending claims differ because the instant claims require 500 mg of irinotecan base per mmol phospholipid, whereas the copending claims recite 500-550 mg of irinotecan base per mmol phospholipid. Nevertheless, the range of the copending claims overlaps with that of the instant claims, resulting in a prima facie case of obviousness-type non-statutory double patenting.

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

The examiner notes that instant claims and the copending claims are understood to have the same effective filing date of 2 May 2005 when provisional applications are **not** taken into account, as this is the actual filing date of application 11/121,294, upon which the instant application and the copending application ultimately claim benefit. As such, the double patenting rejection cannot be withdrawn on the grounds that the copending claims have not yet been issued. See MPEP 804(I)(B)(1)(b)(ii), which states the following:

> If both applications are actually filed on the same day, or are entitled to the same earliest effective filing date taking into account any benefit under 35 U.S.C. 120, 121, 365(c), or 386(c)) with respect to the conflicting claims (see paragraph (a) Effective U.S. filing date, above) the provisional nonstatutory double patenting rejection made in each application should be maintained until the rejection is overcome. Applicant can overcome a provisional nonstatutory double patenting rejection in an application by either filing a reply showing that the claims subject to the provisional nonstatutory double patenting rejections are patentably distinct or filing a terminal disclaimer in the pending application.

As such, this double patenting rejection is applied with respect to the instant application.

Reasons for Not Rejecting Claims Over Prior Art

The following is an examiner's statement of reasons for not rejecting the instant claims over prior art.

As relevant prior art, the examiner cites Chou et al. (Journal of Bioscience and Bioengineering, Vol. 95, No. 4, 2003, pages 405-408). This reference has been previously cited in the office action on 14 July 2017. Chou et al. (hereafter referred to as Chou) is drawn to liposomal irinotecan prepared by pH gradient loading, as of Chou, page 405, title and abstract. Nevertheless, Chou differs from the claimed invention because Chou does not teach sucrose octasulfate. Also, the amount of drug taught by Chou is 0.254 mg drug per mg lipid, as of Chou, page 407, right column, last full paragraph. Even assuming a molecular weight of phospholipid of about 790 grams per mole (which is the molecular weight of distearoyl phosphatidylcholine), this is a concentration of

$$\frac{0.254\ mg\ irinotecan}{1\ mg\ lipid} \times \frac{790\ mg\ lipid}{1\ mmol\ lipid} = 200\ \frac{mg\ irinotean}{mmol\ lipid}$$

This amount is still less than the required amount of 500 mg irinotecan per mmol phospholipid. As such, the skilled artisan would have understood that the inclusion of sucrose octasulfate loads over twice the amount of irinotecan that would have been loaded in a liposome that lacks sucrose octasulfate.

As to claim 5, this claim is understood to modify claim 1 to require that the lipid matrix comprise DSPC and PEG-DSPE, and to further require that there be a specific amount of irinotecan base per mmol of DSPC and PEG-DSPE. As DSPC and PEG-

DSPE are known phospholipids, this claim is understood to have appropriate antecedent basis in claim 1.

Response to Notice of Opposition: Applicant filed a RCE on 7 March 2018 which included an information disclosure statement (IDS). This IDS included cites various references including NPL reference #4 entitled "Annex to the Notice of Opposition against European Patent No. 1746976." This document, hereafter referred to as the notice of opposition, provides arguments as to why the claimed invention is allegedly unpatentable. Various arguments in the notice of opposition are addressed below.

The notice of opposition cites the reference Chou et al. (Journal of Bioscience and Bioengineering, Vol. 95, No. 4, 2003, pages 405-408), which was previously included in the file wrapper. Additional points in the notice of opposition are addressed below.

Point #22 of the notice of opposition teaches that Chou teaches a liposome comprising irinotecan, distearoyl phosphatidylcholine or egg phosphatidylcholine, cholesterol, and PEG(2000)-DSPE. The examiner does not dispute this position, but points out that this liposome of Chou lacks sucrose octasulfate.

Point #23 of the notice of opposition states that the patentee (i.e. the applicant in the instant application) has provided no evidence to support unexpected results. The examiner disagrees with this position. The reasons for the examiner's position in this regard are explained in the response to points #25 and #26 below.

Points #25 and #26 of the notice of opposition take the position that the skilled artisan would have been motivated to have substituted sucrose octasulfate in place of

dextran sulfate. Even if, purely *en arguendo*, this is true, that would still be insufficient to reject the instant claims over Chou.[1] This is because the instant claims have achieved a loading of 500 mg of irinotecan per mmol of phospholipids, as of instant claim 1. In contrast, Chou has achieved a loading of only about 200 mg irinotecan per mmol of lipid. There would have been no expectation that substitution of sucrose octasulfate in place of dextran sulfate would have resulted in more than doubling of the concentration of irinotecan inside the lipid matrix (i.e. liposome).

The examiner also notes here that the issue of the concentration of the irinotecan, which is a limitation of instant claim 1, does not appear to have been addressed by the notice of opposition.

The examiner notes here that, according to MPEP 2144.05(II)(A), it is generally not inventive to discover the optimum or workable ranges (e.g. of concentration) by routine experimentation. Nevertheless, it is the examiner's position that this provision of the MPEP does not apply to the instant claims. This is because the claims not only require a specific concentration of irinotecan, the claims also require that this concentration of irinotecan be comprised by the lipid matrix (i.e. liposome). Loading a drug such as irinotecan into a lipid matrix would not have been straightforward or predictable to one of ordinary skill in the art, and the skilled artisan would not have been able to have predictably loaded more irinotecan drug simply by increasing the concentration of irinotecan. This is because addition of more irinotecan to the mixture of

[1] The preceding sentence should not be construed as an admission that the examiner believes it would have been prima facie obvious for the skilled artisan to have substituted sucrose octasulfate in place of dextran sulfate.

reagents would not have necessarily and predictably resulted in said irinotecan being loaded inside the liposome.

The difficulty of loading irinotecan into a liposome is evident as of Chou, which uses dextran sulfate and a transmembrane gradient loading to load irinotecan, as of Chou, paragraph bridging pages 405 and 406. There would have been no need for such a transmembrane gradient if the concentration of irinotecan in the product could have been increased simply by increasing the irinotecan amount in the starting material. The difficulty of loading irinotecan would have been further increased by the low water solubility of irinotecan.

As such, the claimed concentration of irinotecan, should **not** be understood as merely a concentration that could have been manipulated at will by one of ordinary skill in the art at the time the invention was made by routine optimization. This is at least due to the lack of a reasonable expectation that the loaded concentration could have been successfully increased to the claimed amount due to the difficulty of loading irinotecan into a liposome.

Terminal Disclaimers

The terminal disclaimers filed on 16 October 2017 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of the following patents and applications, as listed below, has been reviewed and is accepted.

US Patent 8,147,867;

US Patent 8,329,213;

US Patent 8,658,203;

US Patent 8,703,181;

US Patent 8,992,970;

US Patent 9,492,442;

US Application 15/241106 (now abandoned);

US Application 15/241128 (now US Patent 9,717,724);

US Application 15/296536 (now US Patent 9,737,528);

US Application 15/227631;

US Application 14/966458 (now US Patent 9,782,349);

US Application 14/965140 (now US Patent 9,724,303);

US Application 14/879302 (now US Patent 9,730,891); and

US Application 14/632422 (now US Patent 9,717,723).

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ISAAC SHOMER whose telephone number is (571)270-7671. The examiner can normally be reached on 7:30 AM to 5:00 PM Monday Through Friday.

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

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ISAAC . SHOMER
Primary Examiner
Art Unit 1612

/ISAAC SHOMER/
Primary Examiner, Art Unit 1612

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/227,561	08/03/2016	Keelung Hong	263266-411993	7226

153749 7590 12/10/2018

McNeill Baur PLLC/Ipsen
Ipsen Bioscience, Inc.
125 Cambridge Park Drive
Suite 301
Cambridge, MA 02140

EXAMINER	
SHOMER, ISAAC	

ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
12/10/2018	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):

docketing@mcneillbaur.com
eofficeaction@appcoll.com
patents.us@ipsen.com

Office Action Summary	Application No. 15/227,561	Applicant(s) Hong et al.	
	Examiner ISAAC SHOMER	Art Unit 1612	AIA Status No

-- 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.

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- 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 25 October 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) 21-41 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) 21-41 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 _____ 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).

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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: _____.

DETAILED ACTION

Applicants' arguments, filed 25 October 2018, have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

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

Claim Interpretation

The instant claims recite the term "lipid matrix." As best understood by the examiner, the term "lipid matrix" is understood to refer to various lipidic structures. These structures include, but are not limited to, liposomal and/or lipid vesicle structures comprising a phospholipid bilayer and an aqueous interior core. See e.g. page 96, paragraph 0242 of the instant specification, which refers to a liposome as a matrix. Both a liposome and a lipid vesicle are understood to comprise an aqueous core surrounded by at least one lipid bilayer.

Substantial Duplicate Claims

Applicant is advised that should claim 31 be found allowable, claim 35 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing

one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections - 35 USC § 112(d) – Failure to Limit Parent Claim

The following is a quotation of 35 U.S.C. 112(d):

> (d) REFERENCE IN DEPENDENT FORMS.—Subject to subsection (e), a claim in dependent form shall contain a reference to a claim previously set forth and then specify a further limitation of the subject matter claimed. A claim in dependent form shall be construed to incorporate by reference all the limitations of the claim to which it refers.

The following is a quotation of pre-AIA 35 U.S.C. 112, fourth paragraph:

> Subject to the following paragraph [i.e., the fifth paragraph of pre-AIA 35 U.S.C. 112], a claim in dependent form shall contain a reference to a claim previously set forth and then specify a further limitation of the subject matter claimed. A claim in dependent form shall be construed to incorporate by reference all the limitations of the claim to which it refers.

Claim 35 is rejected under 35 U.S.C. 112(d) or pre-AIA 35 U.S.C. 112, 4th paragraph, as being of improper dependent form for failing to further limit the subject matter of the claim upon which it depends, or for failing to include all the limitations of the claim upon which it depends. This is because claim 35 depends upon claim 31, but recites the same limitations that were already recited by claim 31. Applicant may cancel the claim(s), amend the claim(s) to place the claim(s) in proper dependent form, rewrite the claim(s) in independent form, or present a sufficient showing that the dependent claim(s) complies with the statutory requirements.

Claim Rejections - 35 USC § 103 – Obviousness

The following is a quotation of pre-AIA 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, 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.

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 pre-AIA 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.

This application currently names joint inventors. In considering patentability of the claims under pre-AIA 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 pre-AIA 35 U.S.C. 103(c) and potential pre-AIA 35 U.S.C. 102(e), (f) or (g) prior art under pre-AIA 35 U.S.C. 103(a).

Claims 21-41 is/are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Chou et al. (Journal of Bioscience and Bioengineering, Vol. 95 No. 4, 2003, pages 405-408) in view of Schlessinger et al. (US Patent 5,783,568).

Chou et al. (hereafter referred to as Chou) is drawn to liposomal irinotecan, as of Chou, page 405, title and abstract.

Chou does not teach sucrose octasulfate.

Schlessinger et al. (hereafter referred to as Schlessinger) is drawn to treatment of cancer or other proliferative diseases. Schlessinger teaches administration of a salt of sucrose octasulfate for treating cancer or abnormal angiogenic cell proliferation, as of Schlessinger, column 27 line 19 to column 28 line 2.

Schlessinger does not teach a liposome comprising irinotecan.

It would have been prima facie obvious for one of ordinary skill in the art to have combined sucrose octasulfate, as of Schlessinger, with the liposome of Chou. The liposome of Chou comprises irinotecan, and is intended for the treatment of cancer. Sucrose octasulfate is also useful for the treatment of cancer, as taught by Schlessinger. As such, it would have been prima facie obvious for one of ordinary skill in the art to have combined sucrose octasulfate, as of Schlessinger, with the irinotecan containing liposome of Chou for predictable treatment of cancer with a reasonable expectation of success. Combining prior art elements (e.g. the irinotecan liposome of Chou and sucrose octasulfate, as of Schlessinger) according to known methods to yield predictable results is prima facie obvious. See MPEP 2143, Exemplary Rationale A.

As to claim 21, the claim requires a total amount of irinotecan of up to about 500 mg per mmol of total phospholipids. Chou teaches an amount of drug (irinotecan) of 0.254 mg drug per mg lipid, as of Chou, page 407, right column, last full paragraph. Even assuming a molecular weight of phospholipid of about 790 grams per mole (which is the molecular weight of distearoyl phosphatidylcholine), this is a concentration of

$$\frac{0.254\ mg\ irinotecan}{1\ mg\ lipid} \times \frac{790\ mg\ lipid}{1\ mmol\ lipid} = 200\ \frac{mg\ irinotean}{mmol\ lipid}$$

This concentration is understood to be within the claimed range.

As to claim 22, this claim further limits the method by which the amount of irinotecan is calculated. As best understood by the examiner, the calculation performed above utilizes irinotecan base, as the molecular weight of irinotecan is calculated as the compound itself, and not as a salt with another anion.

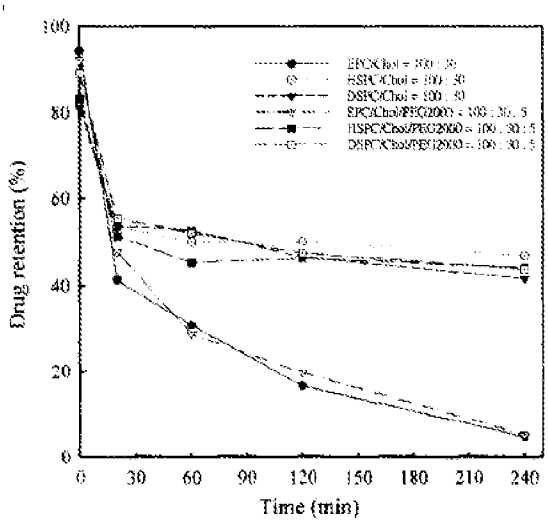
As to claim 23, the calculation above shows about 200 mg of irinotecan per mmol of total phospholipids. This is within the claim scope.

As to claim 24, Chou teaches various phosphatidylcholines, as of Chou, page 406, left column. These phospholipids are understood to be neutral. While phosphatidylcholines are charged, they are zwitterionic, meaning that they include both a positive and a negative charge. These charges balance out to form a compound that is neutral.

As to claim 25, Chou teaches liposomes comprising phosphatidylcholines and cholesterol, as of Chou, page 406, right column, second paragraph. Said phosphatidylcholines read on the required lecithin.

As to claim 26, Chou teaches a liposome of EPC/DSPE-PEG/cholesterol, as of Chou, page 406, right column, second paragraph. This reads on the claimed requirements, wherein EPC is a lecithin and DSPE-PEG is a pegylated lipid.

As to claim 27, Chou teaches DSPE/Chol/PEG2000 liposomes at a ratio of 100:30:5, as of Chou, page 406, figure 1, reproduced below.



While the amounts of the lipids are not exactly the same as those recited by the instant claims, the skilled artisan would have been motivated to have optimized the amount of each lipid in the liposome. Where 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. See MPEP 2144.05(II)(A). In this case, the general conditions of the claim are understood to be taught by the prior art because a liposome comprising irinotecan, DSPC, cholesterol, and DSPE-PEG is taught by Chou. As such, the skilled artisan would have been motivated to have optimized the amount of each lipid ingredient. Additionally, there is a motivation to optimize result effective variables. See MPEP 2144.05(II)(B). In this case, the DSPC and cholesterol have the result of forming the structure of a membrane of a liposome, and the DSPE-PEG has the result of protecting such a liposome from early clearance by the reticuloendothelial system. As such, the concentrations of these lipids are understood to be result-effective variables.

As to claim 28, Chou teaches DSPC. See the above rejection of claim 27.

As to claim 29, Chou teaches a liposome size of between 80 nm and 140 nm, as of Chou, page 405, right column, end of last full paragraph. While the prior art does not

disclose the exact claimed values, but does overlap: in such instances even a slight overlap in range establishes a *prima facie* case of obviousness. See MPEP 2144.05(I).

As to claim 30, this is an independent claim reciting the subject matter of claim 21 but also reciting cholesterol, as well as requiring that 90% of the irinotecan is associated with the lipid matrix. Chou teaches cholesterol, as of Chou, page 406, right column, as explained in the above rejection of claim 27 among other claims. Additionally, Chou teaches encapsulation of the irinotecan in the liposome, resulting in the entirety of the irinotecan being "associated" with the liposome.

As to claim 31, this claim is rejected for the same reason that claim 22 is rejected.

As to claim 32, this claim is rejected for the same reason that claim 23 is rejected.

As to claim 33, this claim is rejected for the same reason that claim 26 is rejected.

As to claim 34, Chou teaches DSPE-PEG as of page 406, right column, first full paragraph.

As to claim 35, this claim is rejected for the same reason that claim 31 is rejected.

As to claim 36, Chou teaches about 200 mg of irinotecan per mmol of lipid, as explained in the above rejection of claim 21. Chou also teaches DSPC and PEG-DSPE, as of Chou, page 406, right column.

As to claim 37, Chou teaches a size range of about 80 nm to 140 nm, as of Chou, page 405, right column, bottom paragraph. This overlaps with the claimed

requirements. While the prior art does not disclose the exact claimed values, but does overlap: in such instances even a slight overlap in range establishes a *prima facie* case of obviousness. See MPEP 2144.05(I).

As to claim 38, this is an independent claim requiring the subject matter of claims 21 and 30 but also specifically reciting the presence of DSPC, cholesterol, and PEG-DSPE, wherein these lipids are recited by instant claims 27 and 34. As such, this claim is rejected for the same reason that claims 30 and 34 are rejected.

As to claim 39, this claim is rejected for the same reason that claims 31 and 35 are rejected.

As to claim 40, this claim is rejected for the same reason that claims 23 and 32 are rejected.

As to claim 41, this claim is rejected for the same reason that claims 29 and 37 are rejected.

Non-Statutory 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 21-41 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 21-36 of copending Application No. 15/896,389 (reference application). Although the claims at issue are not identical, they are not patentably distinct from each other because of the following reasons:

The instant claims are drawn to an injectable pharmaceutical composition comprising irinotecan associated with a lipid matrix as irinotecan sucrose octasulfate.

Copending claim 21 is drawn to a method of delivering irinotecan to a patient having a tumor, the method comprising intravenously administering a liposomal dispersion comprising lipid vesicles comprising a sucrose octasulfate salt of irinotecan.

The instant and copending claims differ because the instant claims are composition claims, and the copending claims are method claims. Nevertheless, the method of the copending claims entails administering a composition, and that composition renders the instant claims obvious for the reasons set forth above and below. As such, there is still a prima facie case of obviousness-type non-statutory double patenting despite the fact that the instant claims are composition claims whereas the copending claims are method claims.

The instant and copending claims appear to differ because the instant claims recite a "lipid matrix", whereas the copending claims recite a liposomal dispersion. Nevertheless, as best understood by the examiner, a liposomal dispersion is a form of a lipid matrix. See the above section of this office action entitled "claim interpretation."

The instant and copending claims also differ because the instant claims recite an amount of irinotecan of up to about 500 mg per total mmol of phospholipids. In contrast, the copending claims recite about 500-550 mg of irinotecan per mmol of phospholipids. Nevertheless, the skilled artisan would have been motivated to have optimized the amount of irinotecan in the copending claims to render it to have been within the scope of the instant claims.

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

Claims 21-41 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 21-33 of copending Application No. 15/896,436 (reference application). Although the claims at issue are not identical, they are not patentably distinct from each other because of the following reasons:

The instant claims are drawn to an injectable pharmaceutical composition comprising irinotecan associated with a lipid matrix as irinotecan sucrose octasulfate.

The copending claims are drawn to a composition comprising lipid vesicles of a liposomal dispersion comprising encapsulated irinotecan and a sulfated sugar which may be sucrose octasulfate.

The instant and copending claims appear to differ because the instant claims recite a "lipid matrix", whereas the copending claims recite a liposomal dispersion. Nevertheless, as best understood by the examiner, a liposomal dispersion is a form of a lipid matrix. See the above section of this office action entitled "claim interpretation."

The instant and copending claims also differ because the instant claims recite an amount of irinotecan of up to about 500 mg per total mmol of phospholipids. In contrast, the copending claims do not appear to recite an amount of irinotecan per mmol of phospholipids. Nevertheless, the skilled artisan would have been motivated to have optimized the amount of irinotecan in the copending claims to render it to have been within the scope of the instant claims.

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

Claims 21-41 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 160-179 of copending Application No. 15/664,976 (reference application). Although the claims at issue are not identical, they are not patentably distinct from each other because of the following reasons:

The instant claims are drawn to an injectable pharmaceutical composition comprising irinotecan associated with a lipid matrix as irinotecan sucrose octasulfate.

The copending claims are drawn to a liposome composition comprising irinotecan sucrose octasulfate. Specific parameters of the effect of this composition on administration to female Albino rats are recited by the copending claims.

The instant and copending claims appear to differ because the instant claims recite a "lipid matrix", whereas the copending claims recite a liposomal dispersion. Nevertheless, as best understood by the examiner, a liposomal dispersion is a form of a lipid matrix. See the above section of this office action entitled "claim interpretation."

The instant and copending claims also differ because the instant claims recite an amount of irinotecan of up to about 500 mg per total mmol of phospholipids. In contrast, the copending claims do not appear to recite an amount of irinotecan per mmol of phospholipids. Nevertheless, the skilled artisan would have been motivated to have optimized the amount of irinotecan in the copending claims to render it to have been within the scope of the instant claims.

The instant and copending claims differ because the copending claims recite various limitations that are not recited by the instant claims. Nevertheless, the issue with regard to double patenting is whether the instant claims would have been obvious over the subject matter of the copending claims. As such, that the copending claims recite limitations not recited by the instant claims does not overcome the applied double patenting rejection.

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

Response to Arguments

In applicant's response on 25 October 2018, applicant has argued that the claimed amendments overcome the applied rejections. In response, the examiner takes the position that applicant's amended claims were reconsidered by the examiner, and the relevant rejections have been presented above.

Terminal Disclaimers

The terminal disclaimers filed on 16 October 2017 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of the following patents and applications, as listed below, has been reviewed and is accepted.

US Patent 8,147,867;

US Patent 8,329,213;

US Patent 8,658,203;

US Patent 8,703,181;

US Patent 8,992,970;

US Patent 9,492,442;

US Application 15/241106 (now abandoned);

US Application 15/241128 (now US Patent 9,717,724);

US Application 15/296536 (now US Patent 9,737,528);

US Application 15/227631;

US Application 14/966458 (now US Patent 9,782,349);

US Application 14/965140 (now US Patent 9,724,303);

US Application 14/879302 (now US Patent 9,730,891); and

US Application 14/632422 (now US Patent 9,717,723).

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ISAAC SHOMER whose telephone number is (571)270-7671. The examiner can normally be reached on 7:30 AM to 5:00 PM Monday Through Friday.

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, Frederick F Krass can be reached on (571)272-0580. 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.

ISAAC . SHOMER
Primary Examiner
Art Unit 1612

/ISAAC SHOMER/
Primary Examiner, Art Unit 1612

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/227,631	08/03/2016	Keelung Hong	263266-411998	9450

139696 7590 07/17/2017

Honigman Miller Schwartz and Cohn LLP/Ipsen
350 East Michigan Avenue, Suite 300
Kalamazoo, MI 49007

EXAMINER	
SHOMER, ISAAC	

ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
07/17/2017	ELECTRONIC

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

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

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

patents@honigman.com
lzerby@honigman.com
anelson@honigman.com

Office Action Summary	Application No. 15/227,631	Applicant(s) HONG ET AL.	
	Examiner ISAAC SHOMER	Art Unit 1612	AIA (First Inventor to File) Status No

-- 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 *3 August 2016*.

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

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

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; 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) *1-20* is/are pending in the application.

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

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-20* 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 _____ 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: _____.

DETAILED ACTION

Notice of Pre-AIA or AIA Status

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

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.

Claim Interpretation

The instant claims use the term “lipid matrix.” As best understood by the examiner, the term “lipid matrix” is understood to refer to various lipidic structures. These structures include, but are not limited to, liposomal and/or lipid vesicle structures comprising a phospholipid bilayer and an aqueous interior core. See e.g. page 96, paragraph 0242 of the instant specification, which refers to a liposome as a matrix.

Non-Statutory 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 1-20 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-35 of U.S. Patent No. 8,147,867 in view of Kirpotin (US Patent 6,110,491).

The instant claims are drawn to a lipid matrix composition comprising phospholipids, sucrose octasulfate, and irinotecan, at a specific size of 110 nm. The claims require a range of 500 to 550 mg irinotecan per mmol of phospholipids.

Conflicting claim 1 is drawn to a liposomal irinotecan composition that also includes sucrose octasulfate. The claims recite about 550 mg of irinotecan per mmol of neutral phospholipids.

The conflicting claims do not recite the required liposome size.

Kirpotin is drawn to liposomes comprising an encapsulated compound, as of Kirpotin, title and abstract. Liposomes of Kirpotin are most preferably sized from about 0.03 to 0.2 microns (30 nm to 200 nm), as of Kirpotin, column 1, lines 1-12.

It would have been prima facie obvious for one of ordinary skill in the art to have sized the liposomes of the conflicting claims in the range taught by Kirpotin. The liposomes of the conflicting claims are used for drug delivery of irinotecan with sucrose octasulfate. However, the conflicting claims are silent as to the liposome size. As

Kirpotin teaches a size range of 30 nm to 200 nm as a useful size range for liposomes that are used to delivery drugs, the skilled artisan would have been motivated to have sized the liposomes of the conflicting claims in the size range taught by Kirpotin. This size range overlaps with the claimed size range, resulting in a prima facie case of obviousness-type non-statutory double patenting.

Claims 1-20 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-17 of U.S. Patent No. 8,329,213 in view of Kirpotin (US Patent 6,110,491).

The instant claims are drawn to a lipid matrix composition comprising phospholipids, sucrose octasulfate, and irinotecan, at a specific size of 110 nm. The claims require a range of 500 to 550 mg irinotecan per mmol of phospholipids.

The conflicting claims are drawn to a liposome comprising irinotecan and sucrose octasulfate, as of conflicting claim 11. Liposomes are understood to comprise phospholipids.

The conflicting claims do not recite the required liposome size.

Kirpotin is drawn to liposomes comprising an encapsulated compound, as of Kirpotin, title and abstract. Liposomes of Kirpotin are most preferably sized from about 0.03 to 0.2 microns (30 nm to 200 nm), as of Kirpotin, column 1, lines 1-12.

It would have been prima facie obvious for one of ordinary skill in the art to have sized the liposomes of the conflicting claims in the range taught by Kirpotin. The

liposomes of the conflicting claims are used for drug delivery of irinotecan with sucrose octasulfate. However, the conflicting claims are silent as to the liposome size. As Kirpotin teaches a size range of 30 nm to 200 nm as a useful size range for liposomes that are used to delivery drugs, the skilled artisan would have been motivated to have sized the liposomes of the conflicting claims in the size range taught by Kirpotin. This size range overlaps with the claimed size range, resulting in a prima facie case of obviousness-type non-statutory double patenting.

The instant and conflicting claims differ because the instant claims recite 500 mg of irinotecan per mmol of total lipid matrix phospholipids. In contrast, conflicting claim 12 recites a ratio of 0.05 to 0.3 mmol irinotecan to mmol phospholipid. Given an irinotecan molecular weight of about 586 mg/mmol, this is about 29 mg irinotecan to 176 mg irinotecan per mmol of lipids. Nevertheless, the skilled artisan would have been motivated to have optimized the amount of irinotecan to have been delivered in order to most effectively have treated the patient to whom the liposomal composition was to have been administered with a reasonable expectation of success. As such, this small difference in the amount of irinotecan fails to overcome the case of obviousness-type non-statutory double patenting.

Claims 1-20 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-17 of U.S. Patent No. 8,703,181 in view of Kirpotin (US Patent 6,110,491).

The instant claims are drawn to a lipid matrix composition comprising phospholipids, sucrose octasulfate, and irinotecan, at a specific size of 110 nm. The claims require a range of 500 to 550 mg irinotecan per mmol of phospholipids.

The conflicting claims are drawn to a method of delivering an antineoplastic agent, including irinotecan, as of conflicting claim 11. This method involves using a liposome comprising irinotecan and sucrose octasulfate. As such, the composition used in the method of the conflicting claims appears to include the components used in the instantly claimed liposome.

The conflicting claims do not recite the required liposome size.

Kirpotin is drawn to liposomes comprising an encapsulated compound, as of Kirpotin, title and abstract. Liposomes of Kirpotin are most preferably sized from about 0.03 to 0.2 microns (30 nm to 200 nm), as of Kirpotin, column 1, lines 1-12.

It would have been prima facie obvious for one of ordinary skill in the art to have sized the liposomes of the conflicting claims in the range taught by Kirpotin. The liposomes of the conflicting claims are used for drug delivery of irinotecan with sucrose octasulfate. However, the conflicting claims are silent as to the liposome size. As Kirpotin teaches a size range of 30 nm to 200 nm as a useful size range for liposomes that are used to delivery drugs, the skilled artisan would have been motivated to have sized the liposomes of the conflicting claims in the size range taught by Kirpotin. This size range overlaps with the claimed size range, resulting in a prima facie case of obviousness-type non-statutory double patenting.

The instant and conflicting claims differ because the instant claims recite 500 mg of irinotecan per mmol of total lipid matrix phospholipids. In contrast, conflicting claim 12 recites a ratio of 0.05 to 0.3 mmol irinotecan to mmol phospholipid. Given an irinotecan molecular weight of about 586 mg/mmol, this is about 29 mg irinotecan to 176 mg irinotecan per mmol of lipids. Nevertheless, the skilled artisan would have been motivated to have optimized the amount of irinotecan to have been delivered in order to most effectively have treated the patient to whom the liposomal composition was to have been administered with a reasonable expectation of success. As such, this small difference in the amount of irinotecan fails to overcome the case of obviousness-type non-statutory double patenting.

Claims 1-20 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-14 of U.S. Patent No. 8,992,970 in view of Kirpotin (US Patent 6,110,491).

The instant claims are drawn to a lipid matrix composition comprising phospholipids, sucrose octasulfate, and irinotecan, at a specific size of 110 nm. The claims require a range of 500 to 550 mg irinotecan per mmol of phospholipids.

The conflicting claims are drawn to liposomes comprising phospholipids, irinotecan, sucrose octasulfate, and a substituted ammonium compound used for loading the irinotecan.

The conflicting claims do not recite the required liposome size.

Kirpotin is drawn to liposomes comprising an encapsulated compound, as of Kirpotin, title and abstract. Liposomes of Kirpotin are most preferably sized from about 0.03 to 0.2 microns (30 nm to 200 nm), as of Kirpotin, column 1, lines 1-12.

It would have been prima facie obvious for one of ordinary skill in the art to have sized the liposomes of the conflicting claims in the range taught by Kirpotin. The liposomes of the conflicting claims are used for drug delivery of irinotecan with sucrose octasulfate. However, the conflicting claims are silent as to the liposome size. As Kirpotin teaches a size range of 30 nm to 200 nm as a useful size range for liposomes that are used to delivery drugs, the skilled artisan would have been motivated to have sized the liposomes of the conflicting claims in the size range taught by Kirpotin. This size range overlaps with the claimed size range, resulting in a prima facie case of obviousness-type non-statutory double patenting.

The instant claims require 500 mg of irinotecan per mmol of lipids. Conflicting claim 9 recites a molar ratio of irinotecan to lipids of at least 1.0. Given a molecular weight of irinotecan of about 586 mg/mmol, this is an amount of about 586 mg of irinotecan per mmol of lipids. While this amount slightly exceeds the claimed concentration of irinotecan, the skilled artisan would have been motivated to have optimized the amount of irinotecan to have been delivered in order to most effectively have treated the patient to whom the liposomal composition was to have been administered with a reasonable expectation of success. As such, this small difference in the amount of irinotecan fails to overcome the case of obviousness-type non-statutory double patenting.

Claims 1-20 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-22 of U.S. Patent No. 8,658,203 in view of Kirpotin (US Patent 6,110,491).

The instant claims are drawn to a lipid matrix composition comprising phospholipids, sucrose octasulfate, and irinotecan, at a specific size of 110 nm. The claims require a range of 500 to 550 mg irinotecan per mmol of phospholipids.

The conflicting claims are drawn to a method of administration of a composition for treating a brain tumor. This composition used in this method is a liposomal composition comprising phospholipids, irinotecan and sucrose octasulfate. The amount of irinotecan is 500 grams per mole of phospholipid, as of conflicting claim 3, which is equivalent to 500 mg per mmol of phospholipid.

The conflicting claims do not recite the required liposome size.

Kirpotin is drawn to liposomes comprising an encapsulated compound, as of Kirpotin, title and abstract. Liposomes of Kirpotin are most preferably sized from about 0.03 to 0.2 microns (30 nm to 200 nm), as of Kirpotin, column 1, lines 1-12.

It would have been prima facie obvious for one of ordinary skill in the art to have sized the liposomes of the conflicting claims in the range taught by Kirpotin. The liposomes of the conflicting claims are used for drug delivery of irinotecan with sucrose octasulfate. However, the conflicting claims are silent as to the liposome size. As Kirpotin teaches a size range of 30 nm to 200 nm as a useful size range for liposomes that are used to delivery drugs, the skilled artisan would have been motivated to have

sized the liposomes of the conflicting claims in the size range taught by Kirpotin. This size range overlaps with the claimed size range, resulting in a prima facie case of obviousness-type non-statutory double patenting.

Claims 1-20 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-30 of U.S. Patent No. 9,492,442.

The instant claims are drawn to a lipid matrix composition comprising phospholipids, sucrose octasulfate, and irinotecan, at a specific size of 110 nm. The claims require a range of 500 to 550 mg irinotecan per mmol of phospholipids.

The conflicting claims are drawn to a method for treating pancreatic cancer. The method of the conflicting claims utilizes a liposome comprising irinotecan sucrose octasulfate, as well as phospholipids and cholesterol, as of conflicting claim 3. Liposome size is from 80 nm to 140 nm, as of conflicting claim 1.

The instant and conflicting claims differ because the instant claims are drawn to a composition, whereas the conflicting claims are drawn to a method. Nevertheless, the composition used in the method of the conflicting claims appears to be essentially the same as the composition of the instantly claimed invention. As such, this results in a prima facie case of non-statutory double patenting.

Note Regarding Apparent Common Assignment: The examiner notes that while there are no common inventors between the instant application and the ‘442 patent, there does appear to be a common assignment. Both the instant application and

the '442 patent appear to be assigned to Ipsen Biopharm Ltd. (Although the printing of the '442 patent discloses that the assignee is Merrimack Pharmaceuticals, the assignment appears to have been changed to Ipsen Biopharm Ltd., as of the application data sheet submitted on 05/16/2017 in the file wrapper of application 14/851,111, which is the application that became the '442 patent).

Claims 1-20 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-5, 13, and 24-36 of copending Application No. 14/632,422 (reference application – currently allowed but not yet issued). Although the claims at issue are not identical, they are not patentably distinct from each other because of the following reasons.

The instant claims are drawn to a lipid matrix composition comprising phospholipids, sucrose octasulfate, and irinotecan, at a specific size of 110 nm. The claims require a range of 500 to 550 mg irinotecan per mmol of phospholipids.

The copending claims are drawn to a method of making a liposomal composition of an antineoplastic agent, wherein said antineoplastic agent is irinotecan, as of copending claim 1. Said composition made by the method of the copending claims is a liposomal composition comprising sucrose octasulfate and irinotecan. Liposomes are sized from about 110 nm to about 120 nm, as of copending claim 24. Amounts of

irinotecan range from about 150 to about 550 mg per mmol of liposome lipid, as of copending claim 24.

The instant and copending claims differ because the instant claims are drawn to a composition, whereas the copending claims are drawn to a method of making the composition. Nevertheless, the method of the copending claims would have made a composition that includes all of the features of the instantly claimed composition, resulting in a prima facie case of non-statutory double patenting.

The instant and copending claims differ because the instant claims recite specific values of size and irinotecan concentration, whereas the copending claims recite a range. Nevertheless, the range of the copending claims overlaps with the values required by the instant claims, resulting in a prima facie case of obviousness-type non-statutory double patenting.

Claims 1-20 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-10 and 12-21 of copending Application No. 14/879,302 (reference application – currently allowed but not yet issued). Although the claims at issue are not identical, they are not patentably distinct from each other because of the following reasons.

The instant claims are drawn to a lipid matrix composition comprising phospholipids, sucrose octasulfate, and irinotecan, at a specific size of 110 nm. The claims require a range of 500 to 550 mg irinotecan per mmol of phospholipids.

The copending claims are drawn to a method of treatment comprising parenteral administration of a liposomal irinotecan composition comprising irinotecan sucrose octasulfate, as of copending claim 1. The amount of irinotecan ranges from 150 mg to 500 mg per mmol liposome phospholipids, as of copending claim 1. Liposome size can be about 110 nm to 120 nm, as of copending claim 12(h).

The instant and copending claims differ because the instant claims are drawn to a composition, whereas the copending claims are drawn to a method of using the composition. Nevertheless, the method of the copending claims utilizes a composition that includes all of the features of the instantly claimed composition, resulting in a prima facie case of non-statutory double patenting.

The instant and copending claims differ because the instant claims recite specific values of size and irinotecan concentration, whereas the copending claims recite a range. Nevertheless, the range of the copending claims overlaps with the values required by the instant claims, resulting in a prima facie case of obviousness-type non-statutory double patenting.

Claims 1-20 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1 and 45-63 of copending Application No. 14/965,140 (reference application – currently allowed but not yet issued). Although the claims at issue are not identical, they are not patentably distinct from each other because of the following reasons.

The instant claims are drawn to a lipid matrix composition comprising phospholipids, sucrose octasulfate, and irinotecan, at a specific size of 110 nm. The claims require a range of 500 to 550 mg irinotecan per mmol of phospholipids.

Copending claim 1 is drawn to an irinotecan sucrose octasulfate in lipid vesicles. These lipid vesicles may include phospholipids, as of copending claim 45, and the amount of irinotecan is 500 mg per mmol of phospholipids, as of copending claim 45. Liposomes have a size of about 110 nm, as of copending claim 63.

The instant and copending claims differ because no single copending claim recites all of the features of the instant claims. For example, copending claim 63 recites the required liposome size but also recites a concentration range of irinotecan that overlaps with but does not read on the claimed size requirements. As such, there is no case of statutory double patenting. Nevertheless, the copending claims recite all of the subject matter required by the instant claims in separate copending claims, resulting in a prima facie case of non-statutory double patenting.

Claims 1-20 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-3, 5-11, and 17-23 of copending Application No. 14/966,458 (reference application – currently allowed but not yet issued) in view of Kirpotin (US Patent 6,110,491).

The instant claims are drawn to a lipid matrix composition comprising phospholipids, sucrose octasulfate, and irinotecan, at a specific size of 110 nm. The claims require a range of 500 to 550 mg irinotecan per mmol of phospholipids.

Copending claim 1 is drawn to a liposome comprising irinotecan and a sulfated sugar in a lipid vesicle. Said sulfate sugar may be sucrose octasulfate, as of copending claim 6.

The copending claims are silent as to liposome size.

Kirpotin is drawn to liposomes comprising an encapsulated compound, as of Kirpotin, title and abstract. Liposomes of Kirpotin are most preferably sized from about 0.03 to 0.2 microns (30 nm to 200 nm), as of Kirpotin, column 1, lines 1-12.

It would have been prima facie obvious for one of ordinary skill in the art to have sized the liposomes of the conflicting claims in the range taught by Kirpotin. The liposomes of the conflicting claims are used for drug delivery of irinotecan with sucrose octasulfate. However, the conflicting claims are silent as to the liposome size. As Kirpotin teaches a size range of 30 nm to 200 nm as a useful size range for liposomes that are used to delivery drugs, the skilled artisan would have been motivated to have sized the liposomes of the conflicting claims in the size range taught by Kirpotin. This size range overlaps with the claimed size range, resulting in a prima facie case of obviousness-type non-statutory double patenting.

The copending claims are silent as to the amount of irinotecan in the composition. Nevertheless, the copending claims recite that irinotecan is present. As such, the skilled artisan would have been motivated to have optimized the concentration of irinotecan, with respect to that of liposome lipids, in order to have predictably optimized the dose of irinotecan to have predictably improved treatment of a patient with a reasonable expectation of success.

Claims 1-20 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-20 of copending Application No. 15/227,561 (reference application). Although the claims at issue are not identical, they are not patentably distinct from each other because of the following reasons.

The instant claims are drawn to a lipid matrix composition comprising phospholipids, sucrose octasulfate, and irinotecan, at a specific size of 110 nm. The claims require a range of 500 to 550 mg irinotecan per mmol of phospholipids.

Copending claim 1 is drawn to a matrix comprising phospholipids, sucrose octasulfate, and irinotecan. Said matrix is sized at a size of 110 nm and has 500 mg of irinotecan per mmol of phospholipids.

As such, the subject matter of the copending claims appears to be within the scope of that of the instant claims, resulting in a prima facie case of anticipatory-type non-statutory double patenting.

Claims 1-20 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claim 1 of copending Application No. 15/296,536 (reference application – currently allowed but not yet issued). Although the claims at issue are not identical, they are not patentably distinct from each other because of the following reasons.

The instant claims are drawn to a lipid matrix composition comprising phospholipids, sucrose octasulfate, and irinotecan, at a specific size of 110 nm. The claims require a range of 500 to 550 mg irinotecan per mmol of phospholipids.

Copending claim 1 is drawn to an irinotecan sucrose octasulfate liposome. Said liposome comprises irinotecan, sucrose octasulfate, and phospholipids among other lipids. Said liposome is sized from 95-110 nm, and has 500-550 mg of irinotecan per total liposome phospholipids.

The instant and copending claims differ as the copending claims recite various features not recited by the instant claims. Nevertheless, the subject matter of the copending claims appears to be within the scope of that of the instant claims, resulting in a prima facie case of anticipatory-type non-statutory double patenting.

Claims 1-20 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-24 of copending Application No. 15/241,128 (reference application – currently allowed but not yet issued) in view of Kirpotin (US Patent 6,110,491).

The instant claims are drawn to a lipid matrix composition comprising phospholipids, sucrose octasulfate, and irinotecan, at a specific size of 110 nm. The claims require a range of 500 to 550 mg irinotecan per mmol of phospholipids.

Copending claim 1 is drawn to a method of treating a type of cancer comprising providing an irinotecan liposome. Copending claim 24 recites that the irinotecan liposome comprises precipitated sucrose octasulfate.

Copending claim 1 is silent as to liposome size.

Kirpotin is drawn to liposomes comprising an encapsulated compound, as of Kirpotin, title and abstract. Liposomes of Kirpotin are most preferably sized from about 0.03 to 0.2 microns (30 nm to 200 nm), as of Kirpotin, column 1, lines 1-12.

It would have been prima facie obvious for one of ordinary skill in the art to have sized the liposomes of the conflicting claims in the range taught by Kirpotin. The liposomes of the conflicting claims are used for drug delivery of irinotecan with sucrose octasulfate. However, the conflicting claims are silent as to the liposome size. As Kirpotin teaches a size range of 30 nm to 200 nm as a useful size range for liposomes that are used to delivery drugs, the skilled artisan would have been motivated to have sized the liposomes of the conflicting claims in the size range taught by Kirpotin. This size range overlaps with the claimed size range, resulting in a prima facie case of obviousness-type non-statutory double patenting.

The copending claims are silent as to the amount of irinotecan in the composition. Nevertheless, the copending claims recite that irinotecan is present. As such, the skilled artisan would have been motivated to have optimized the concentration of irinotecan, with respect to that of liposome lipids, in order to have predictably optimized the dose of irinotecan to have predictably improved treatment of a patient with a reasonable expectation of success.

Note Regarding Common Assignment: The instant and copending applications do not appear to have common inventors. However, the instant and copending applications do appear to be commonly assigned to Ipsen Biopharm Ltd. As

such, the double patenting rejection is understood to be proper for the reasons set forth above as well as in view of the fact that the instant and copending applications are commonly assigned.

Claims 1-20 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 2 and 4-22 of copending Application No. 15/241,106 (reference application) in view of Kirpotin (US Patent 6,110,491).

The instant claims are drawn to a lipid matrix composition comprising phospholipids, sucrose octasulfate, and irinotecan, at a specific size of 110 nm. The claims require a range of 500 to 550 mg irinotecan per mmol of phospholipids.

Copending claim 19(a) is drawn to a method of treating cancer comprising administering liposomal irinotecan. Copending claim 20(a) recites that the irinotecan liposome comprise sucrose octasulfate and DSPC, which is a phospholipid.

The copending claims are silent as to liposome size.

Kirpotin is drawn to liposomes comprising an encapsulated compound, as of Kirpotin, title and abstract. Liposomes of Kirpotin are most preferably sized from about 0.03 to 0.2 microns (30 nm to 200 nm), as of Kirpotin, column 1, lines 1-12.

It would have been prima facie obvious for one of ordinary skill in the art to have sized the liposomes of the conflicting claims in the range taught by Kirpotin. The

liposomes of the conflicting claims are used for drug delivery of irinotecan with sucrose octasulfate. However, the conflicting claims are silent as to the liposome size. As Kirpotin teaches a size range of 30 nm to 200 nm as a useful size range for liposomes that are used to delivery drugs, the skilled artisan would have been motivated to have sized the liposomes of the conflicting claims in the size range taught by Kirpotin. This size range overlaps with the claimed size range, resulting in a prima facie case of obviousness-type non-statutory double patenting.

The copending claims are silent as to the amount of irinotecan in the composition. Nevertheless, the copending claims recite that irinotecan is present. As such, the skilled artisan would have been motivated to have optimized the concentration of irinotecan, with respect to that of liposome lipids, in order to have predictably optimized the dose of irinotecan to have predictably improved treatment of a patient with a reasonable expectation of success.

Note Regarding Common Assignment: The instant and copending applications do not appear to have common inventors. However, the instant and copending applications do appear to be commonly assigned to Ipsen Biopharm Ltd. As such, the double patenting rejection is understood to be proper for the reasons set forth above as well as in view of the fact that the instant and copending applications are commonly assigned.

Cited Prior Art

As relevant prior art, the examiner cites Chou et al. (Journal of Bioscience and Bioengineering, Vol. 95, No. 4, 2003, pages 405-408). Chou et al. (hereafter referred to as Chou) is drawn to liposomal irinotecan prepared by pH gradient loading, as of Chou, page 405, title and abstract. Nevertheless, Chou differs from the claimed invention because Chou does not teach sucrose octasulfate. Also, the amount of drug taught by Chou is 0.254 mg drug per mg lipid, as of Chou, page 407, right column, last full paragraph. Even assuming a molecular weight of phospholipid of about 790 grams per mole (which is the molecular weight of distearoyl phosphatidylcholine), this is a concentration of

$$\frac{0.254\ mg\ irinotecan}{1\ mg\ lipid} \times \frac{790\ mg\ lipid}{1\ mmol\ lipid} = 200\ \frac{mg\ irinotean}{mmol\ lipid}$$

This amount is still less than the lower limit of 500 mg irinotecan per mmol phospholipid. As such, the skilled artisan would have understood that the inclusion of sucrose octasulfate loads over twice the amount of irinotecan that would have been loaded in a liposome that lacks sucrose octasulfate.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ISAAC SHOMER whose telephone number is (571)270-7671. The examiner can normally be reached on 8:00 AM - 5:00 PM Monday-Friday.

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, Frederick F. Krass can be reached on (571)272-0580. 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.

/ISAAC SHOMER/
Primary Examiner, Art Unit 1612

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McNeill Baur PLLC/Ipsen
Ipsen Bioscience, Inc.
125 Cambridge Park Drive
Suite 301
Cambridge, MASSACHUSETTS 02140
UNITED STATES OF AMERICA

EXAMINER
SHOMER, ISAAC

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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.

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docketing@mcneillbaur.com
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patents.us@ipsen.com

Office Action Summary	Application No. 15/227,631	Applicant(s) Hong et al.	
	Examiner ISAAC SHOMER	Art Unit 1612	AIA Status No

-- 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 01 March 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) 1-20 is/are pending in the application.

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

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 1-20 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 _____ 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: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after allowance. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, prosecution in this application has been reopened pursuant to 37 CFR 1.114.

Applicant's submission filed on 1 March 2018 has been entered, and the arguments presented therein have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

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

Claim Interpretation

The instant claims recite the term “lipid matrix.” As best understood by the examiner, the term “lipid matrix” is understood to refer to various lipidic structures. These structures include, but are not limited to, liposomal and/or lipid vesicle structures comprising a phospholipid bilayer and an aqueous interior core. See e.g. page 96, paragraph 0242 of the instant specification, which refers to a liposome as a matrix. Both a liposome and a lipid vesicle are understood to comprise an aqueous core surrounded by at least one lipid bilayer.

Statutory Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process... may obtain a patent therefor..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the claims that are directed to the same invention so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 1-20 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-20 of copending Application No. 15/896,436 (reference application). This is a provisional statutory double patenting rejection since the claims directed to the same invention have not in fact been patented.

Non-Statutory 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 1-20 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-20 of copending Application No. 15/896,389 (reference application). Although the claims at issue are not identical, they are not patentably distinct from each other because of the following reasons:

The instant claims are drawn to a pharmaceutical composition comprising irinotecan sucrose octasulfate precipitated in a lipid matrix having a size of 110 nm. The composition comprises about 500-550 mg of irinotecan per mmol of total phospholipids.

The copending claims are drawn to a pharmaceutical composition comprising irinotecan sucrose octasulfate precipitated in a lipid matrix having a size of 110 nm. The composition comprises about 500 of irinotecan per mmol of total phospholipids.

The instant and copending claims differ because the instant claims recite 500-550 mg of irinotecan per mmol phospholipid, whereas the copending claims recite 500 mg of irinotecan per mmol of phospholipids. Nevertheless, the copending claims are within the scope of the instant claims, thereby effectively anticipating the instant claims. This results in a prima facie case of anticipatory-type non-statutory double patenting.

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

The examiner notes that instant claims and the copending claims are understood to have the same effective filing date of 2 May 2005 when provisional applications are **not** taken into account, as this is the actual filing date of application 11/121,294, upon which the instant application and the copending application ultimately claim benefit. As such, the double patenting rejection cannot be withdrawn on the grounds that the copending claims have not yet been issued. See MPEP 804(I)(B)(1)(b)(ii), which states the following:

> If both applications are actually filed on the same day, or are entitled to the same earliest effective filing date taking into account any benefit under 35 U.S.C. 120, 121, 365(c), or 386(c)) with respect to the conflicting claims (see paragraph (a) Effective U.S. filing date, above) the provisional nonstatutory double patenting rejection made in each application should be maintained until the rejection is overcome. Applicant can overcome a provisional nonstatutory double patenting rejection in an application by either filing a reply showing that the claims subject to the provisional nonstatutory double patenting rejections are patentably distinct or filing a terminal disclaimer in the pending application.

As such, this double patenting rejection is applied with respect to the instant application.

Reasons for Not Rejecting Claims Over Prior Art

The following is an examiner's statement of reasons for not rejecting the instant claims over prior art.

As relevant prior art, the examiner cites Chou et al. (Journal of Bioscience and Bioengineering, Vol. 95, No. 4, 2003, pages 405-408). This reference has been previously cited in the office action on 17 July 2017. Chou et al. (hereafter referred to as

Chou) is drawn to liposomal irinotecan prepared by pH gradient loading, as of Chou, page 405, title and abstract. Nevertheless, Chou differs from the claimed invention because Chou does not teach sucrose octasulfate. Also, the amount of drug taught by Chou is 0.254 mg drug per mg lipid, as of Chou, page 407, right column, last full paragraph. Even assuming a molecular weight of phospholipid of about 790 grams per mole (which is the molecular weight of distearoyl phosphatidylcholine), this is a concentration of

$$\frac{0.254\ mg\ irinotecan}{1\ mg\ lipid} \times \frac{790\ mg\ lipid}{1\ mmol\ lipid} = 200\ \frac{mg\ irinotean}{mmol\ lipid}$$

This amount is still less than the lower limit of 500 mg irinotecan per mmol phospholipid. As such, the skilled artisan would have understood that the inclusion of sucrose octasulfate loads over twice the amount of irinotecan that would have been loaded in a liposome that lacks sucrose octasulfate.

As to claim 4, this claim is understood to modify claim 1 to require that the lipid matrix comprise DSPC and PEG-DSPE, and to further require that there be a specific amount of irinotecan base per mmol of DSPC and PEG-DSPE. As DSPC and PEG-DSPE are known phospholipids, this claim is understood to have appropriate antecedent basis in claim 1.

Response to Notice of Opposition: Applicant filed a RCE on 1 March 2018 which included an information disclosure statement (IDS). This IDS included cites various references including NPL reference #4 entitled “Annex to the Notice of Opposition against European Patent No. 1746976.” This document, hereafter referred to as the notice of opposition, provides arguments as to why the claimed invention is

allegedly unpatentable. Various arguments in the notice of opposition are addressed below.

The notice of opposition cites the reference Chou et al. (Journal of Bioscience and Bioengineering, Vol. 95, No. 4, 2003, pages 405-408), which was previously included in the file wrapper. Additional points in the notice of opposition are addressed below.

Point #22 of the notice of opposition teaches that Chou teaches a liposome comprising irinotecan, distearoyl phosphatidylcholine or egg phosphatidylcholine, cholesterol, and PEG(2000)-DSPE. The examiner does not dispute this position, but points out that this liposome of Chou lacks sucrose octasulfate.

Point #23 of the notice of opposition states that the patentee (i.e. the applicant in the instant application) has provided no evidence to support unexpected results. The examiner disagrees with this position. The reasons for the examiner's position in this regard are explained in the response to points #25 and #26 below.

Points #25 and #26 of the notice of opposition take the position that the skilled artisan would have been motivated to have substituted sucrose octasulfate in place of dextran sulfate. Even if, purely *en arguendo*, this is true, that would still be insufficient to reject the instant claims over Chou.[1] This is because the instant claims have achieved a loading of 500-550 mg of irinotecan per mmol of phospholipids, as of instant claim 1. In contrast, Chou has achieved a loading of only about 200 mg irinotecan per mmol of lipid. There would have been no expectation that substitution of sucrose octasulfate in

[1] The preceding sentence should not be construed as an admission that the examiner believes it would have been prima facie obvious for the skilled artisan to have substituted sucrose octasulfate in place of dextran sulfate.

place of dextran sulfate would have resulted in more than doubling of the concentration of irinotecan inside the lipid matrix (i.e. liposome).

The examiner also notes here that the issue of the concentration of the irinotecan, which is a limitation of instant claim 1, does not appear to have been addressed by the notice of opposition.

The examiner notes here that, according to MPEP 2144.05(II)(A), it is generally not inventive to discover the optimum or workable ranges (e.g. of concentration) by routine experimentation. Nevertheless, it is the examiner's position that this provision of the MPEP does not apply to the instant claims. This is because the claims not only require a specific concentration of irinotecan, the claims also require that this concentration of irinotecan be comprised by the lipid matrix (i.e. liposome). Loading a drug such as irinotecan into a lipid matrix would not have been straightforward or predictable to one of ordinary skill in the art, and the skilled artisan would not have been able to have predictably loaded more irinotecan drug simply by increasing the concentration of irinotecan. This is because addition of more irinotecan to the mixture of reagents would not have necessarily and predictably resulted in said irinotecan being loaded inside the liposome.

The difficulty of loading irinotecan into a liposome is evident as of Chou, which uses dextran sulfate and a transmembrane gradient loading to load irinotecan, as of Chou, paragraph bridging pages 405 and 406. There would have been no need for such a transmembrane gradient if the concentration of irinotecan in the product could have been increased simply by increasing the irinotecan amount in the starting material. The

difficulty of loading irinotecan would have been further increased by the low water solubility of irinotecan.

As such, the claimed concentration of irinotecan, should **not** be understood as merely a concentration that could have been manipulated at will by one of ordinary skill in the art at the time the invention was made by routine optimization. This is at least due to the lack of a reasonable expectation that the loaded concentration could have been successfully increased to the claimed amount due to the difficulty of loading irinotecan into a liposome.

Terminal Disclaimers

The terminal disclaimers filed on 16 October 2017 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of the patents and applications listed below has been reviewed and is accepted.

US Patent 8,147,867;

US Patent 8,329,213;

US Patent 8,703,181;

US Patent 8,992,970;

US Patent 8,658,203;

US Patent 9,492,442;

US Application 14/632,422 (now US Patent 9,717,723);

US Application 14/879,302 (now US Patent 9,730,891);

US Application 14/965,140 (now US Patent 9,724,303);

US Application 14/966,458 (now US Patent 9,782,349);

US Application 15/227,561;

US Application 15/296,536 (now US Patent 9,737,528);

US Application 15/241,128 (now US Patent 9,717,724); and

US Application 15/241,106.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ISAAC SHOMER whose telephone number is (571)270-7671. The examiner can normally be reached on 7:30 AM to 5:00 PM Monday Through Friday.

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, Frederick F Krass can be reached on (571)272-0580. 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.

ISAAC . SHOMER
Primary Examiner
Art Unit 1612

/ISAAC SHOMER/
Primary Examiner, Art Unit 1612

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/227,631	08/03/2016	Keelung Hong	263266-411998	9450

153749 7590 08/31/2018

McNeill Baur PLLC/Ipsen
Ipsen Bioscience, Inc.
125 Cambridge Park Drive
Suite 301
Cambridge, MA 02140

EXAMINER	
SHOMER, ISAAC	

ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
08/31/2018	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):

docketing@mcneillbaur.com
eofficeaction@appcoll.com
patents.us@ipsen.com

Office Action Summary	Application No. 15/227,631	Applicant(s) Hong et al.	
	Examiner ISAAC SHOMER	Art Unit 1612	AIA Status No

-- 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 10 August 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 and 19 is/are pending in the application.

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

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 1-17 and 19 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 _____ 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: _____.

DETAILED ACTION

Applicants' arguments, filed 10 August 2018, have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

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

This action is NON-FINAL.

Claim Interpretation

The instant claims recite the term "lipid matrix." As best understood by the examiner, the term "lipid matrix" is understood to refer to various lipidic structures. These structures include, but are not limited to, liposomal and/or lipid vesicle structures comprising a phospholipid bilayer and an aqueous interior core. See e.g. page 96, paragraph 0242 of the instant specification, which refers to a liposome as a matrix. Both a liposome and a lipid vesicle are understood to comprise an aqueous core surrounded by at least one lipid bilayer.

Non-Statutory 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 1-17 and 19 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 21-34 of copending Application No. 15/896,436 (reference application). Although the claims at issue are not identical, they are not patentably distinct from each other because of the following reasons:

The instant claims are drawn to a pharmaceutical composition comprising irinotecan sucrose octasulfate gelated or precipitated in a lipid matrix. The instant claims recite an approximate particle size and an approximate amount of irinotecan.

Copending claim 21 is drawn to lipid vesicles as a liposomal dispersion. The lipid vesicles comprise irinotecan and a sulfated sugar polyanion that may be sucrose octasulfate.

The instant and copending claims differ because the instant claims recite a particle size and an amount of irinotecan, which is not recited by the copending claims. Nevertheless, the composition of the instant claims appears to be within the scope of that of the copending claims. As such, the subject matter of the instant claims is effectively anticipated by that of the copending claims. This results in a prima facie case of anticipatory-type non-statutory double patenting.

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

The examiner notes that the instant and copending claims have the same effective filing date of 2 May 2005 (excluding provisional applications). As the instant and copending claims have the same effective filing date, the provisional rejection will be maintained until the rejection is overcome, either by the filing of a terminal disclaimer or by a persuasive argument showing that the copending claims are patentably distinct from the instant claims. See MPEP 804(I)(B)(1)(b)(ii), which states the following.

> If both applications are actually filed on the same day, or are entitled to the same earliest effective filing date taking into account any benefit under 35 U.S.C. 120, 121, 365(c), or 386(c)) with respect to the conflicting claims (see paragraph (a) Effective U.S. filing date, above) the provisional nonstatutory double patenting rejection made in each application should be maintained until the rejection is overcome. Applicant can overcome a provisional nonstatutory double patenting rejection in an application by either filing a reply showing that the claims subject to the provisional nonstatutory double patenting rejections are patentably distinct or filing a terminal disclaimer in the pending application.

As such, the double patenting rejection is not withdrawn.

Response to Arguments: In applicant's response on 10 August 2018, applicant argues that because claims 1-20 of the copending application, which were previously rejection, are now cancelled, this rejection is moot. No additional argument is presented.

This is not persuasive because the rejection of the newly added claims is applicable for the reasons set forth above.

Claims 1-17 and 19 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 21-36 of copending Application No. 15/896,389 (reference application). Although the claims at issue are not identical, they are not patentably distinct from each other because of the following reasons:

The instant claims are drawn to a pharmaceutical composition comprising irinotecan sucrose octasulfate gelated or precipitated in a lipid matrix. The instant claims recite an approximate particle size and an approximate amount of irinotecan.

Copending claim 21 is drawn to method for delivering irinotecan to a patient having a tumor. Said method utilizes drawn to lipid vesicles as a liposomal dispersion. The lipid vesicles comprise irinotecan and a sulfated sugar polyanion that may be sucrose octasulfate.

The instant and copending claims differ because the instant claims are drawn to a composition and the copending claims are drawn to a method. Nevertheless, the method of the copending claims utilize a specific composition, and the instantly claimed composition is within the scope of the composition used by the copending method claims. As such, that the instant claims are composition claims and the copending claims are method claims is insufficient to overcome the applied double patenting rejection.

The instant and copending claims differ because the instant claims recite a particle size and an amount of irinotecan, which is not recited by the copending claims. Nevertheless, the composition of the instant claims appears to be within the scope of that of the copending claims. As such, the subject matter of the instant claims is

effectively anticipated by that of the copending claims. This results in a prima facie case of anticipatory-type non-statutory double patenting.

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

The examiner notes that the instant and copending claims have the same effective filing date of 2 May 2005 (excluding provisional applications). As the instant and copending claims have the same effective filing date, the provisional rejection will be maintained until the rejection is overcome, either by the filing of a terminal disclaimer or by a persuasive argument showing that the copending claims are patentably distinct from the instant claims. See MPEP 804(I)(B)(1)(b)(ii), which is explained in greater detail in the above rejection.

Claims 1-17 and 19 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 160-179 of copending Application No. 15/664,976 (reference application). Although the claims at issue are not identical, they are not patentably distinct from each other because of the following reasons:

The instant claims are drawn to a pharmaceutical composition comprising irinotecan sucrose octasulfate gelated or precipitated in a lipid matrix. The instant claims recite an approximate particle size and an approximate amount of irinotecan.

Copending claim 160 is drawn to a liposome comprising irinotecan sucrose octasulfate. Copending claim 174 recites a particle size of about 110 nm, which is the

same as instantly claimed. The copending claims recite specific functional parameters regarding administration to female Albino rats.

The instant and copending claims differ because the copending claims do not recite the requirement of about 500-550 mg irinotecan base per total mmol of phospholipids. However, copending claim 1628 recites 0.15-1.5 mol if irinotecan per mol of lipid. As the molecular weight of irinotecan is about 586.7 Daltons for the free base of irinotecan, this is about 88-880 mg of irinotecan per mmol of lipid. This appears to overlap with the claimed amount of about 550 mg of irinotecan per mmol of total phospholipid. This results in a prima facie case of obviousness-type non-statutory double patenting.

The instant and copending claims differ because the copending claims recite various functional properties regarding administration to female Albino rats that are not recited by the instant claims. However, it appears that the claimed composition is within the scope of that of the copending application. As such, the skilled artisan would have expected the claimed composition to have had the required functional properties regarding administration to female Albino rats even if this property was not explicitly recited by the instant claims.

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

Reasons for Not Rejecting Claims Over Prior Art

The following is an examiner's statement of reasons for not rejecting the instant claims over prior art. This rationale is essentially the same as that provided by the examiner in the office action on 10 April 2018.

As relevant prior art, the examiner cites Chou et al. (Journal of Bioscience and Bioengineering, Vol. 95, No. 4, 2003, pages 405-408). This reference has been previously cited in the office action on 17 July 2017. Chou et al. (hereafter referred to as Chou) is drawn to liposomal irinotecan prepared by pH gradient loading, as of Chou, page 405, title and abstract. Nevertheless, Chou differs from the claimed invention because Chou does not teach sucrose octasulfate. Also, the amount of drug taught by Chou is 0.254 mg drug per mg lipid, as of Chou, page 407, right column, last full paragraph. Even assuming a molecular weight of phospholipid of about 790 grams per mole (which is the molecular weight of distearoyl phosphatidylcholine), this is a concentration of

$$\frac{0.254\ mg\ irinotecan}{1\ mg\ lipid} \times \frac{790\ mg\ lipid}{1\ mmol\ lipid} = 200\ \frac{mg\ irinotean}{mmol\ lipid}$$

This amount is still less than the lower limit of 500 mg irinotecan per mmol phospholipid. As such, the skilled artisan would have understood that the inclusion of sucrose octasulfate loads over twice the amount of irinotecan that would have been loaded in a liposome that lacks sucrose octasulfate.

As to claim 4, this claim is understood to modify claim 1 to require that the lipid matrix comprise DSPC and PEG-DSPE, and to further require that there be a specific amount of irinotecan base per mmol of DSPC and PEG-DSPE. As DSPC and PEG-

DSPE are known phospholipids, this claim is understood to have appropriate antecedent basis in claim 1.

Response to Notice of Opposition: Applicant filed a RCE on 1 March 2018 which included an information disclosure statement (IDS). This IDS included cites various references including NPL reference #4 entitled "Annex to the Notice of Opposition against European Patent No. 1746976." This document, hereafter referred to as the notice of opposition, provides arguments as to why the claimed invention is allegedly unpatentable. Various arguments in the notice of opposition are addressed below.

The notice of opposition cites the reference Chou et al. (Journal of Bioscience and Bioengineering, Vol. 95, No. 4, 2003, pages 405-408), which was previously included in the file wrapper. Additional points in the notice of opposition are addressed below.

Point #22 of the notice of opposition teaches that Chou teaches a liposome comprising irinotecan, distearoyl phosphatidylcholine or egg phosphatidylcholine, cholesterol, and PEG(2000)-DSPE. The examiner does not dispute this position, but points out that this liposome of Chou lacks sucrose octasulfate.

Point #23 of the notice of opposition states that the patentee (i.e. the applicant in the instant application) has provided no evidence to support unexpected results. The examiner disagrees with this position. The reasons for the examiner's position in this regard are explained in the response to points #25 and #26 below.

Points #25 and #26 of the notice of opposition take the position that the skilled artisan would have been motivated to have substituted sucrose octasulfate in place of

dextran sulfate. Even if, purely *en arguendo*, this is true, that would still be insufficient to reject the instant claims over Chou.[1] This is because the instant claims have achieved a loading of 500-550 mg of irinotecan per mmol of phospholipids, as of instant claim 1. In contrast, Chou has achieved a loading of only about 200 mg irinotecan per mmol of lipid. There would have been no expectation that substitution of sucrose octasulfate in place of dextran sulfate would have resulted in more than doubling of the concentration of irinotecan inside the lipid matrix (i.e. liposome).

The examiner also notes here that the issue of the concentration of the irinotecan, which is a limitation of instant claim 1, does not appear to have been addressed by the notice of opposition.

The examiner notes here that, according to MPEP 2144.05(II)(A), it is generally not inventive to discover the optimum or workable ranges (e.g. of concentration) by routine experimentation. Nevertheless, it is the examiner's position that this provision of the MPEP does not apply to the instant claims. This is because the claims not only require a specific concentration of irinotecan, the claims also require that this concentration of irinotecan be comprised by the lipid matrix (i.e. liposome). Loading a drug such as irinotecan into a lipid matrix would not have been straightforward or predictable to one of ordinary skill in the art, and the skilled artisan would not have been able to have predictably loaded more irinotecan drug simply by increasing the concentration of irinotecan. This is because addition of more irinotecan to the mixture of

[1] The preceding sentence should not be construed as an admission that the examiner believes it would have been prima facie obvious for the skilled artisan to have substituted sucrose octasulfate in place of dextran sulfate.

reagents would not have necessarily and predictably resulted in said irinotecan being loaded inside the liposome.

The difficulty of loading irinotecan into a liposome is evident as of Chou, which uses dextran sulfate and a transmembrane gradient loading to load irinotecan, as of Chou, paragraph bridging pages 405 and 406. There would have been no need for such a transmembrane gradient if the concentration of irinotecan in the product could have been increased simply by increasing the irinotecan amount in the starting material. The difficulty of loading irinotecan would have been further increased by the low water solubility of irinotecan.

As such, the claimed concentration of irinotecan, should **not** be understood as merely a concentration that could have been manipulated at will by one of ordinary skill in the art at the time the invention was made by routine optimization. This is at least due to the lack of a reasonable expectation that the loaded concentration could have been successfully increased to the claimed amount due to the difficulty of loading irinotecan into a liposome.

Terminal Disclaimers

The terminal disclaimers filed on 16 October 2017 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of the patents and applications listed below has been reviewed and is accepted.

US Patent 8,147,867;

US Patent 8,329,213;

US Patent 8,703,181;

US Patent 8,992,970;

US Patent 8,658,203;

US Patent 9,492,442;

US Application 14/632,422 (now US Patent 9,717,723);

US Application 14/879,302 (now US Patent 9,730,891);

US Application 14/965,140 (now US Patent 9,724,303);

US Application 14/966,458 (now US Patent 9,782,349);

US Application 15/227,561;

US Application 15/296,536 (now US Patent 9,737,528);

US Application 15/241,128 (now US Patent 9,717,724); and

US Application 15/241,106 (now abandoned).

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ISAAC SHOMER whose telephone number is (571)270-7671. The examiner can normally be reached on 7:30 AM to 5:00 PM Monday Through Friday.

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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, Frederick F Krass can be reached on (571)272-0580. 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.

ISAAC . SHOMER
Primary Examiner
Art Unit 1612

/ISAAC SHOMER/
Primary Examiner, Art Unit 1612

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/227,631	08/03/2016	Keelung Hong	263266-411998	9450

153749 7590 12/19/2018

McNeill Baur PLLC/Ipsen
Ipsen Bioscience, Inc.
125 Cambridge Park Drive
Suite 301
Cambridge, MA 02140

EXAMINER	
SHOMER, ISAAC	

ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
12/19/2018	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):

docketing@mcneillbaur.com
eofficeaction@appcoll.com
patents.us@ipsen.com

Office Action Summary	Application No. 15/227,631	Applicant(s) Hong et al.	
	Examiner ISAAC SHOMER	Art Unit 1612	AIA Status No

-- 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 30 November 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) 21-41 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) 21-41 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 _____ 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: _____.

DETAILED ACTION

Applicants' arguments, filed 30 November 2018, have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

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

Claim Interpretation

The instant claims recite the term "lipid matrix." As best understood by the examiner, the term "lipid matrix" is understood to refer to various lipidic structures. These structures include, but are not limited to, liposomal and/or lipid vesicle structures comprising a phospholipid bilayer and an aqueous interior core. See e.g. page 96, paragraph 0242 of the instant specification, which refers to a liposome as a matrix. Both a liposome and a lipid vesicle are understood to comprise an aqueous core surrounded by at least one lipid bilayer.

Non-Statutory 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 21-41 provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 21-36 of copending Application No. 15/896,389 (reference application). Although the claims at issue are not identical, they are not patentably distinct from each other because of the following reasons:

The instant claims are drawn to a lipid matrix comprising irinotecan and sucrose octasulfate, wherein the lipid matrix comprises one or more phospholipids. The term "lipid matrix" is understood to be a lipidic structure that may be a liposome. The claims require irinotecan in an amount of about 500 mg to 550 mg per mmol of total phospholipids.

Copending claim 21 is drawn to a method for delivering irinotecan to a tumor. The method of conflicting claim 21 entails administering a liposomal dispersion of lipid vesicles comprising sucrose octasulfate and irinotecan. Conflicting claims 35 and 36 recite an amount of about 500-550 mg irinotecan per mmol of phospholipid.

The instant and copending claims differ because the instant claims are drawn to a composition, whereas the copending claims are drawn to methods. Nevertheless, the composition used in the method of the copending claims appears to be essentially the same as that recited by the instant claims. As such, the composition of the copending

claims effectively anticipates that of the instant claims, resulting in a prima facie case of anticipatory-type non-statutory double patenting.

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

Claims 21-41 provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 21-34 of copending Application No. 15/896,436 (reference application). Although the claims at issue are not identical, they are not patentably distinct from each other because of the following reasons:

The instant claims are drawn to a lipid matrix comprising irinotecan and sucrose octasulfate, wherein the lipid matrix comprises one or more phospholipids. The term "lipid matrix" is understood to be a lipidic structure that may be a liposome. The claims require irinotecan in an amount of about 500 mg to 550 mg per mmol of total phospholipids.

Copending claim 21 is drawn to a liposomal dispersion encapsulating irinotecan and a sulfated sugar which may be sucrose octasulfate. Copending claims 24 and 25 recite at least 0.5 mg of irinotecan per mg of total lipids.

The instant and copending claims differ because the instant claims recite an amount of about 500 mg to 550 mg of irinotecan per mmol of total phospholipids. This is not recited by the copending claims. In contrast, the copending claims recite at least 0.5 mg of irinotecan per mg of total lipids. However, copending claim 30 recites that the lipid

is distearoyl phosphatidylcholine (DSPC). This has a molecular weight of 790.15 Daltons. As such, the examiner performs the following calculation:

$$\frac{0.5\ mg\ irinotecan}{1\ mg\ lipid} \times \frac{790.15\ mg\ lipid}{1\ mmol\ lipid} \approx 395\ \frac{mg\ irinotecan}{mmol\ lipid}$$

As such, the copending claims require an amount of at least about 395 mg irinotecan per mmol lipid. This overlaps with the claimed requirement of an amount of about 500 mg to about 550 mg of irinotecan per mmol of total phospholipids. This overlap results in a prima facie case of obviousness-type non-statutory double patenting.

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

Claims 21-41 provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 160-179 of copending Application No. 15/664,976 (reference application). Although the claims at issue are not identical, they are not patentably distinct from each other because of the following reasons:

The instant claims are drawn to a lipid matrix comprising irinotecan and sucrose octasulfate, wherein the lipid matrix comprises one or more phospholipids. The term "lipid matrix" is understood to be a lipidic structure that may be a liposome. The claims require irinotecan in an amount of about 500 mg to 550 mg per mmol of total phospholipids.

Copending claim 160 is drawn to a liposome comprising irinotecan sucrose octasulfate. The irinotecan is a hydrochloride. Specific pharmacokinetic parameters are recited by the claim.

The instant and copending claims differ because the copending claims do not recite a total amount of irinotecan of about 500 mg to 550 mg per mmol of total phospholipids. Nevertheless, copending claim 162 recites a composition containing from about 0.15 to about 1.5 moles of irinotecan per mol of lipid. The molecular weight of irinotecan in the hydrochloride form is about 623 g/mol. As such, the examiner has performed the following calculations.

$$\frac{0.15\,mol\ irinotecan}{1\,mol\ lipid} \times \frac{623\ g}{1\,mol} \times \frac{1000\ mg}{1\,gram} \times \frac{1\,mol}{1000\ mmol} \approx 93\ \frac{mg\ irinotecan}{mmol\ lipid}$$

$$\frac{1.5\,mol\ irinotecan}{1\,mol\ lipid} \times \frac{623\ g}{1\,mol} \times \frac{1000\ mg}{1\,gram} \times \frac{1\,mol}{1000\ mmol} \approx 934\ \frac{mg\ irinotecan}{mmol\ lipid}$$

As such, the amount of irinotecan in terms of mg of irinotecan per mmol of lipid ranges from about 93 to about 934 mg irinotecan per mmmol lipid. This overlaps with the claimed amount of about 500 to 550 mg of irinotecan per mmol lipid, resulting in a prima facie case of obviousness-type non-statutory double patenting.

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

Reasons for Not Rejecting Claims Over Prior Art

The following is an examiner's statement of reasons for not rejecting the instant claims over prior art. This rationale is essentially the same as that provided by the examiner in the office action on 31 August 2018.

As relevant prior art, the examiner cites Chou et al. (Journal of Bioscience and Bioengineering, Vol. 95, No. 4, 2003, pages 405-408). This reference has been previously cited in the office action on 17 July 2017. Chou et al. (hereafter referred to as Chou) is drawn to liposomal irinotecan prepared by pH gradient loading, as of Chou, page 405, title and abstract. Nevertheless, Chou differs from the claimed invention because Chou does not teach sucrose octasulfate. Also, the amount of drug taught by Chou is 0.254 mg drug per mg lipid, as of Chou, page 407, right column, last full paragraph. Even assuming a molecular weight of phospholipid of about 790 grams per mole (which is the molecular weight of distearoyl phosphatidylcholine), this is a concentration of

$$\frac{0.254\ mg\ irinotecan}{1\ mg\ lipid} \times \frac{790\ mg\ lipid}{1\ mmol\ lipid} = 200\ \frac{mg\ irinotean}{mmol\ lipid}$$

This amount is less than the lower limit of 500 mg irinotecan per mmol phospholipid required by all of the instant claims. As such, the skilled artisan would have understood that the inclusion of sucrose octasulfate loads over twice the amount of irinotecan that would have been loaded in a liposome that lacks sucrose octasulfate.

Response to Notice of Opposition: Applicant filed a RCE on 1 March 2018 which included an information disclosure statement (IDS). This IDS included cites various references including NPL reference #4 entitled "Annex to the Notice of Opposition against European Patent No. 1746976." This document, hereafter referred to

as the notice of opposition, provides arguments as to why the claimed invention is allegedly unpatentable. Various arguments in the notice of opposition are addressed below.

The notice of opposition cites the reference Chou et al. (Journal of Bioscience and Bioengineering, Vol. 95, No. 4, 2003, pages 405-408), which was previously included in the file wrapper. Additional points in the notice of opposition are addressed below.

Point #22 of the notice of opposition teaches that Chou teaches a liposome comprising irinotecan, distearoyl phosphatidylcholine or egg phosphatidylcholine, cholesterol, and PEG(2000)-DSPE. The examiner does not dispute this position, but points out that this liposome of Chou lacks sucrose octasulfate.

Point #23 of the notice of opposition states that the patentee (i.e. the applicant in the instant application) has provided no evidence to support unexpected results. The examiner disagrees with this position. The reasons for the examiner's position in this regard are explained in the response to points #25 and #26 below.

Points #25 and #26 of the notice of opposition take the position that the skilled artisan would have been motivated to have substituted sucrose octasulfate in place of dextran sulfate. Even if, purely *en arguendo*, this is true, that would still be insufficient to reject the instant claims over Chou.[1] This is because the instant claims have achieved a loading of 500-550 mg of irinotecan per mmol of phospholipids, as required by the instant claims. In contrast, Chou has achieved a loading of only about 200 mg irinotecan

[1] The preceding sentence should not be construed as an admission that the examiner believes it would have been prima facie obvious for the skilled artisan to have substituted sucrose octasulfate in place of dextran sulfate.

per mmol of lipid. There would have been no expectation that substitution of sucrose octasulfate in place of dextran sulfate would have resulted in more than doubling of the concentration of irinotecan inside the lipid matrix (i.e. liposome).

The examiner also notes here that the issue of the concentration of the irinotecan, which is a limitation of the instant claims, does not appear to have been addressed by the notice of opposition.

The examiner notes here that, according to MPEP 2144.05(II)(A), it is generally not inventive to discover the optimum or workable ranges (e.g. of concentration) by routine experimentation. Nevertheless, it is the examiner's position that this provision of the MPEP does not apply to the instant claims. This is because the claims not only require a specific concentration of irinotecan, the claims also require that this concentration of irinotecan be comprised by the lipid matrix (i.e. liposome). Loading a drug such as irinotecan into a lipid matrix would not have been straightforward or predictable to one of ordinary skill in the art, and the skilled artisan would not have been able to have predictably loaded more irinotecan drug simply by increasing the concentration of irinotecan. This is because addition of more irinotecan to the mixture of reagents would not have necessarily and predictably resulted in said irinotecan being loaded inside the liposome.

The difficulty of loading irinotecan into a liposome is evident as of Chou, which uses dextran sulfate and a transmembrane gradient loading to load irinotecan, as of Chou, paragraph bridging pages 405 and 406. There would have been no need for such a transmembrane gradient if the concentration of irinotecan in the product could have been increased simply by increasing the irinotecan amount in the starting material. The

difficulty of loading irinotecan would have been further increased by the low water solubility of irinotecan.

As such, the claimed concentration of irinotecan, should **not** be understood as merely a concentration that could have been manipulated at will by one of ordinary skill in the art at the time the invention was made by routine optimization. This is at least due to the lack of a reasonable expectation that the loaded concentration could have been successfully increased to the claimed amount due to the difficulty of loading irinotecan into a liposome.

Terminal Disclaimers

The terminal disclaimers filed on 16 October 2017 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of the patents and applications listed below has been reviewed and is accepted.

US Patent 8,147,867;

US Patent 8,329,213;

US Patent 8,703,181;

US Patent 8,992,970;

US Patent 8,658,203;

US Patent 9,492,442;

US Application 14/632,422 (now US Patent 9,717,723);

US Application 14/879,302 (now US Patent 9,730,891);

US Application 14/965,140 (now US Patent 9,724,303);

US Application 14/966,458 (now US Patent 9,782,349);

US Application 15/227,561;

US Application 15/296,536 (now US Patent 9,737,528);

US Application 15/241,128 (now US Patent 9,717,724); and

US Application 15/241,106 (now abandoned).

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ISAAC SHOMER whose telephone number is (571)270-7671. The examiner can normally be reached on 7:30 AM to 5:00 PM Monday Through Friday.

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, Frederick F Krass can be reached on (571)272-0580. 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.

ISAAC . SHOMER
Primary Examiner
Art Unit 1612

/ISAAC SHOMER/
Primary Examiner, Art Unit 1612

Electronic Acknowledgement Receipt

EFS ID:	35142166
Application Number:	15809815
International Application Number:	
Confirmation Number:	5137
Title of Invention:	Methods for Treating Metastatic Pancreatic Cancer Using Combination Therapies Comprising Liposomal Irinotecan and Oxaliplatin
First Named Inventor/Applicant Name:	Eliel Bayever
Customer Number:	153749
Filer:	Mary Rucker Henninger/richard king
Filer Authorized By:	Mary Rucker Henninger
Attorney Docket Number:	263266-421428
Receipt Date:	13-FEB-2019
Filing Date:	10-NOV-2017
Time Stamp:	18:52:23
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Non Patent Literature	Kim__2012__poster.pdf	695166 c5fe55f9ccc75bcaaf4fc9db1a30e6fef0ca6315	no	8

Warnings:

Information:					
2	Non Patent Literature	Klinz__2011__poster.pdf	1091734 0835675af4c742d17baa2bf78197c43c841d2605	no	8
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3	Non Patent Literature	Ko_2013.pdf	567651 45f71034d319081c5cfcc40d359e69cebe72054b	no	6
Warnings:					
Information:					
4	Non Patent Literature	Ma__2015__poster.pdf	809793 7c82e115e831eca2872cd876236a1b1c248fb2d7	no	7
Warnings:					
Information:					
5	Non Patent Literature	Mathe__1989.pdf	1909817 d647fd52256ffc20d86b564aadb9912dc4062b01	no	14
Warnings:					
Information:					
6	Non Patent Literature	Mizuno_2013_abst.pdf	99984 a2836992222bd2128981f58546b3a629475e4347	no	2
Warnings:					
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7	Foreign Reference	PCTUS2016047727_IPRP.pdf	222620 94ba46da71ec2dc8d071e36031e24998955c90a3	no	6
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Information:					
8	Foreign Reference	PCTUS2016047727_ISR_WO.pdf	305923 602d5701c0cc3e227f551134b448a441eb2ece02	no	8
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Information:					

9	Non Patent Literature	VonHoff__2014__poster.pdf	881983 0aff7cb065ef160322662ff748556586c11513d8	no	11
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10	Other Reference-Patent/App/Search documents	US11121294_2009-08-17_OA.pdf	1195467 b51e88a6118459042680a4e6aeeff45b00cd6fd5	no	33
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11	Other Reference-Patent/App/Search documents	US11121294_2010-03-12_OA.pdf	521092 9ee672eb9bf7d812d5444d2ff42d2f417b4becf1	no	15
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12	Other Reference-Patent/App/Search documents	US11121294_2010-05-19_AA.pdf	124726 293deabb4e7108eacea37f7171d241ae8eec713b	no	3
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13	Other Reference-Patent/App/Search documents	US11121294_2010-08-04_OA.pdf	489107 b58b0488a4bef9cb64b59415af2a45c41b9f3fee	no	14
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14	Other Reference-Patent/App/Search documents	US11121294_2010-12-06_OA.pdf	587111 cbf846beed40e16f4050d18014fdd1177594e0fb	no	17
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15	Other Reference-Patent/App/Search documents	US11121294_2011-04-13_OA.pdf	321810 887e9860d2264aeb57d98e0dc16d97c5a44b08cd	no	10
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16	Other Reference-Patent/App/Search documents	US11121294_2011-07-12_Int_Sum.pdf	162678 4684142483a212d57c146edc6fcde09ae0361ae0	no	3
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17	Other Reference-Patent/App/Search documents	US11121294_2011-11-23_OA.pdf	716308 a3b891223486d74b952f22b7f969eb5bb40e07f5	no	20
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18	Other Reference-Patent/App/Search documents	US11601451_2010-01-11_OA.pdf	505358 160601eab9f0d424056196a84a6f2e003ff1e74e	no	14
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19	Other Reference-Patent/App/Search documents	US11601451_2010-08-27_OA.pdf	634527 f1074ab3d67a128acce2fa421ccedcbb2915ba0a	no	17
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20	Other Reference-Patent/App/Search documents	US11601451_2011-07-12_Int_Sum.pdf	167312 5d6694d2b7edad484d517022cc1ce97b66a6d9a0	no	4
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Information:					
21	Other Reference-Patent/App/Search documents	US13416204_2012-05-08_OA.pdf	149879 25ffe202c06783ea81c36a40c498c75eb4ab1885	no	4
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22	Other Reference-Patent/App/Search documents	US13416204_2012-06-29_Int_Sum_OA.pdf	287766 b079bc2e63b1a136e122b1bc67607583a12c217f	no	6
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23	Other Reference-Patent/App/Search documents	US13654373_2013-08-12_Int_Sum_OA.pdf	363005 cd35b7878eee7090ebb707dfe8c2c1d108e63623	no	10
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24	Other Reference-Patent/App/Search documents	US14151632_2016-04-18_OA.pdf	339186 ec59b7410d04374ee76dcf01839e232157b58b63	no	9
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25	Other Reference-Patent/App/Search documents	US14175365_2014-06-26_OA.pdf	701699 ee341612254459e0f5054755ebbff3e33944cc58	no	20
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26	Other Reference-Patent/App/Search documents	US14406776_2016-02-26_OA.pdf	344065 52799f555c7648c2ef9b3c81521081af709d3b7e	no	9
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27	Other Reference-Patent/App/Search documents	US14406776_2016-04-25_Resp.pdf	3571305 4fe60edf136c16e8a085af911ac07819b5323433	no	71
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28	Other Reference-Patent/App/Search documents	US14632422_2017-01-10_OA.pdf	586580 20db23173d535af1c23c092bc26d71df0d9c71f9	no	18
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29	Other Reference-Patent/App/Search documents	US14812950_2015-10-02_OA.pdf	120984 7137cd0e8f525a526cf3ec4004af170976282a56	no	3
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30	Other Reference-Patent/App/Search documents	US14812950_2015-10-22_PA.pdf	234276 9b780c04da3b88baf0eb3d5d89475aafc499f234	no	7
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31	Other Reference-Patent/App/Search documents	US14844500_2015-12-16_OA.pdf	910397 8896fa97859c9e113c808ce9d13001c7f24f2f57	no	25
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32	Other Reference-Patent/App/Search documents	US14844500_2016-02-25_Resp.pdf	587372 9d40d5fa801a1553e3d172c23e72c2a4578b9a14	no	15
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33	Other Reference-Patent/App/Search documents	US14851111_2016-02-25_OA.pdf	470983 13faaf6e94e1234aab21d5f75f2aa38368d0c1f0	no	13
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34	Other Reference-Patent/App/Search documents	US14851111_2016-05-12_Resp.pdf	3523603 086b0e2818ea8cd52e3a7a1a3f06ca1657a001ca	no	71
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35	Other Reference-Patent/App/Search documents	US14879302_2016-08-15_OA.pdf	990363 a7650e30dd57d9cb1daf479904a5aad0cfa40c51	no	30
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36	Other Reference-Patent/App/Search documents	US14879302_2016-12-15_OA.pdf	544430 4000aa714da98794ec05a3eb2f84f7bf61b1f4d0	no	14
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37	Other Reference-Patent/App/Search documents	US14879358_2015-12-28_OA.pdf	705313 ef7e3fedfe2322a9fdc03a60b7f40b94be20c1e3	no	20
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Information:					
38	Other Reference-Patent/App/Search documents	US14879358_2016-07-12_OA_Int_Sum.pdf	484896 72fabb990f8402f175094a94ec7e760736ced4f6	no	14
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Information:					
39	Other Reference-Patent/App/Search documents	US14964239_2016-11-04_OA.pdf	807583 2e9145f7a5e0f788433053847cb3ff1e9c8f9112	no	21
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40	Other Reference-Patent/App/Search documents	US14964239_2017-04-26_Int_Sum.pdf	69939 a9a51fa671f793635afdf8299381da7ffb520c95	no	2
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41	Other Reference-Patent/App/Search documents	US14964239_2017-06-21_OA.pdf	586729 777b495c577d8b57ba8bf6f1ad75b8c038836a6e	no	16
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42	Other Reference-Patent/App/Search documents	US14964239_2017-12-11_OA.pdf	407708 f0ac7a088f616f2d3b6e3dfdcfc8905d396aba1f	no	15
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43	Other Reference-Patent/App/Search documents	US14964571_2017-02-13_OA.pdf	337701 016467d6df1f6cb2753f741a58d25efdd930e95d	no	8
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44	Other Reference-Patent/App/Search documents	US14964571_2017-11-01_OA.pdf	427392 ba3384d00f086c7ca791d392d07ba47e8cd8e182	no	14
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45	Other Reference-Patent/App/Search documents	US14964571_2018-09-25_OA.pdf	484999 9492b28a8ad93b9b0ffbd1ead6a7f9b5e8e4dace	no	12
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46	Other Reference-Patent/App/Search documents	US14965140_2016-03-10_OA.pdf	1800290 e418c3094c8bf5b22d1a3e4dd7a86bcfdb122635	no	24
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47	Other Reference-Patent/App/Search documents	US14965140_2016-07-13_OA_Int_Sum.pdf	980240 97c07d04f9f4be890bef1293ff7710379611e8f7	no	14
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48	Other Reference-Patent/App/Search documents	US14965140_2016-12-19_OA.pdf	684321 0d6ddbc4dd7e711fec5d76b7403be450aa55f7b8	no	9
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49	Other Reference-Patent/App/Search documents	US14966458_2016-12-06_OA.pdf	2464089 bc4d4c667b3c2841ccb44ca7137547231fc57bfc	no	34
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50	Other Reference-Patent/App/Search documents	US14966458_2017-04-27_Int_Sum.pdf	131444 2c7ab713c035634fba4afbc88b3ebc697bf460b3	no	2
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51	Other Reference-Patent/App/Search documents	US14979666_2016-12-09_OA.pdf	1534483 bdf958ecc999205c80e572e3c18d77172299b3dc	no	20
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52	Other Reference-Patent/App/Search documents	US15059640_2016-12-02_OA.pdf	637984 510ae46e715ee37c3b59b6fff127e7f4739fd8d0	no	9
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53	Other Reference-Patent/App/Search documents	US15227561_2017-07-14_OA.pdf	1871621 0e9bd74e0dbb2fd237b6809ab5d46a064d1d6fcf	no	25
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Information:					
54	Other Reference-Patent/App/Search documents	US15227561_2018-04-26_OA.pdf	1036785 12080de92323d4f828a16951eedd59f6209401a4	no	13
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55	Other Reference-Patent/App/Search documents	US15227561_2018-12-10_OA.pdf	649875 dcf8606373bacd91ad8f1b428f11069dbcb8a154	no	18
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56	Other Reference-Patent/App/Search documents	US15227631_2017-07-17_OA.pdf	868034 9352e43ce726b743aa24c9c9fa9cb84ff6ff771a	no	24
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57	Other Reference-Patent/App/Search documents	US15227631_2018-04-10_OA.pdf	474150 8675f78b3495aa3ad2153d3f76b6742fcaca54f8	no	13
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58	Other Reference-Patent/App/Search documents	US15227631_2018-08-31_OA.pdf	554554 08cda2dd50e22ee2918fc3768cd87d4d41ffa44d	no	15
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Information:					
59	Other Reference-Patent/App/Search documents	US15227631_2018-12-19_OA.pdf	520182 ea2d9c82cb39a0bee5b95ffbf3cc98167b0626f1	no	15
Warnings:					
Information:					
		Total Files Size (in bytes):	44256372		

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

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

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United States Patent and Trademark Office
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www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/241,106	08/19/2016	Eliel Bayever	239669-401116	4520

133156 7590 10/28/2016

Honigman Miller Schwartz and Cohn LLP
350 East Michigan Avenue
Suite 300
Kalamazoo, MI 49007

EXAMINER	
RONEY, CELESTE A	

ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
10/28/2016	ELECTRONIC

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

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

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

patents@honigman.com
fhunter@honigman.com

Notice of References Cited	Application/Control No. 15/241,106	Applicant(s)/Patent Under Reexamination BAYEVER ET AL.	
	Examiner CELESTE A. RONEY	Art Unit 1612	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	CPC Classification	US Classification
	A	US-				
	B	US-				
	C	US-				
	D	US-				
	E	US-				
	F	US-				
	G	US-				
	H	US-				
	I	US-				
	J	US-				
	K	US-				
	L	US-				
	M	US-				

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	CPC Classification
	N	WO-2016-094402	06-2016		Bayever et al	
	O	WO-2013-188586	12-2013		Bayever et al	
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Fleming DR, Importance of sequence in chemotherapy administration, 10/20/2014; http://www.oncologynurseadvisor.com/advisor-forum/importance-of-sequence-in-chemotherapy-administration/article/378072/
	V	Conroy T, FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer, NEJM, 2011, 364, 1817-1825
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

First Action Interview Pilot Program Pre-Interview Communication	Application No. 15/241,106	Applicant(s) BAYEVER ET AL.	
	Examiner CELESTE A. RONEY	Art Unit 1612	AIA (First Inventor to File) Status Yes

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

THE SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE **ONE MONTH OR THIRTY (30) DAYS,** WHICHEVER IS LONGER, FROM THE MAILING OR NOTIFICATION DATE OF THIS COMMUNICATION.

This time period for reply is extendable under 37 CFR 1.136(a) for only ONE additional MONTH.

This communication constitutes notice under 37 CFR 1.136(a)(1)(i).

Applicant must, within the time period for reply, file: (1) A letter requesting not to have a first action interview; (2) A reply under 37 CFR 1.111 waiving the first action interview and First Action Interview Office Action; or (3) An Applicant Initiated Interview Request Form (PTOL-413A) electronically via EFS-Web, accompanied by a proposed amendment or arguments, and schedule the interview within 2 months from the filing of the request. A failure to respond to this communication will be treated as a request not to have an interview. If applicant waives the First Action Interview Office Action, the instant Pre-Interview Communication is deemed the first Office Action on the Merits. The next subsequent Office action may be made final if appropriate. See MPEP 706.07(a).

Status

1)☒ Responsive to communication(s) filed on *9/26/16, First Action Interview Request*.

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

Disposition of Claims

2)☒ Claim(s) *1-20* is/are pending in the application.

2a) Of the above claim(s) _____ is/are withdrawn from consideration.

3)☐ Claim(s) _____ is/are allowed.

4)☒ Claim(s) ***1-20*** is/are rejected.

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

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

Application Papers

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

8)☐ 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

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

a)☐ All b)☐ Some * c)☐ None of:

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.

Contact Information

Examiner's Telephone Number: (571)272-5192

Examiner's Typical Work Schedule: Monday-Thursday; 7A-4P

Supervisor's Name: Fred Krass

Supervisor's Telephone Number: (571)272-0580

Attachment(s)

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

2) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/6/16, 10/11/16 and 10/13/16*.

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

4) ☐ Other: _____.

First Action Interview Pilot Program Pre-Interview Communication	**Application No.** 15/241,106	**Applicant(s)** BAYEVER ET AL.	
	Examiner CELESTE A. RONEY	**Art Unit** 1612	**AIA (First Inventor to File) Status** Yes

Notification of Rejection(s) and/or Objection(s)

#	Claim(s)	Reference(s) (if applicable)	Rejection Statutory Basis	Brief Explanation of Rejection
1	1-3, 5-8, 10, 16 and 19	O, V	103	Bayever disclosed treatment of pancreatic cancer using recited drugs except oxaliplatin; Conroy disclosed pancreatic cancer treatment with oxaliplatin.
2	11-15, 17 and 20	O, V, N	103	Bayever disclosed the liposome MM-398, but was not specific as to the ingredients. WO 2016/094402 evidenced that MM-398 contained irinotecan sucrose octasulfate, DSPC, cholesterol and MPEG-2000-DSPE.
3	18	O, V, U	103	Bayever and Conroy did not disclose the claimed order of administration. Fleming disclosed that the sequence of chemotherapy drugs does not matter.
4	4 and 9	O, V, U	103	Bayever and Conroy did not disclose the claimed order of administration. Fleming disclosed that the sequence of chemotherapy drugs does not matter.

Expanded Discussion/Commentary

1		It would have been prima facie obvious to have used Conroy's oxaliplatin within Bayever's treatment because oxaliplatin has clinical activity against pancreatic cancer, when combined ith fluorouracil, and because oxaliplatin and irinotecan have synergistic activity, as taught by Conroy.
2		It is reasonable to assume that Bayever's (2013) MM-398 contains irinotecan, DSPC, cholesterol and MPEG-2000-DSPE, as evidenced by Bayever's (2016) disclosure of the liposomal constituents of MM-398.
3		It would have been prima facie obvious to vary the order of administration because the sequence of various chemotherapy drugs in general does not matter, as disclosed by Fleming.
4		It would have been prima facie obvious to vary the order of administration because the sequence of various chemotherapy drugs in general does not matter, as disclosed by Fleming.

DATE: 12 October, 2016	/CELESTE A. RONEY/ Examiner, Art Unit 1612	

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www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/241,106	08/19/2016	Eliel Bayever	239669-401116	4520

133156 7590 12/29/2016

Honigman Miller Schwartz and Cohn LLP
350 East Michigan Avenue
Suite 300
Kalamazoo, MI 49007

EXAMINER
RONEY, CELESTE A

ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
12/29/2016	ELECTRONIC

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

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

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

patents@honigman.com
arhoades@honigman.com
lbroecker@honigman.com

Office Action Summary	Application No. 15/241,106	Applicant(s) BAYEVER ET AL.	
	Examiner CELESTE A. RONEY	Art Unit 1612	AIA (First Inventor to File) Status Yes

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

Period for Reply

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

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

Status

1)☒ Responsive to communication(s) filed on *11/28/16*.

☐ 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) *1-20* is/are pending in the application.

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

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-20* 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 _____ 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 *10/25/16; 11/28/16; 12/8/16; 12/9/16; 12/13/16*.

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

4) ☐ Other: _____.

DETAILED ACTION

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

Claim Rejections - 35 USC § 103

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

> A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-3, 5-8, 10, 16 and 19 are rejected under 35 U.S.C. 103 as being unpatentable over Bayever et al (WO 2013/188586), in view of Conroy et al (NEJM, 34(19), 2011, 1817).

Bayever et al disclosed a method for treatment of pancreatic cancer in a patient (e.g., a human, at page 3, 1st paragraph), comprising co-administering to the patient liposomal irinotecan at a dose of 60 mg/m^2, 5-fluorouracil at a dose of 2400 mg/m^2 and leucovorin (*l* form administered at 200 mg/m^2 or the *l+d* racemic form administered at 400 mg/m^2). The method comprised at least one cycle of administration, wherein the cycle was a period of two weeks (page 3, last full paragraph).

In one embodiment, Bayever's patient population was patients undergoing treatment for metastatic adenocarcinoma pancreatic cancer (e.g. a patient who has not previously received an antineoplastic agent) (page 12, section V, last embodiment, and claim 10).

Bayever did not disclose oxaliplatin, as recited in claim 1.

Conroy disclosed FOLFIRINOX (oxaliplatin, 85 mg per square meter of body-surface area; irinotecan; leucovorin and fluorouracil) treatment of patients having metastatic pancreatic cancer (title and the methods section of the abstract). Conroy disclosed that oxaliplatin has clinical activity against pancreatic cancer only when combined with fluorouracil, and that oxaliplatin and irinotecan have been shown to have synergistic activity in vitro (page 1818, left column, second paragraph).

Conroy did not disclose that the irinotecan was liposomal irinotecan.

Since Bayever disclosed treating metastatic pancreatic carcinoma with 5-fluorouracil and irinotecan, it would have been prima facie obvious to one of ordinary skill in the art to have included oxaliplatin within Bayever's methods of treatment. An ordinarily skilled artisan would have been motivated because oxaliplatin has clinical activity against pancreatic cancer when combined with fluorouracil, and because oxaliplatin and irinotecan have synergistic activity in vitro, as taught by Conroy (Conroy, page 1818, left column, second paragraph).

The combination of Bayever and Conroy reads on claims 1, 16 and 19.

Claims 2 and 3 are rendered prima facie obvious because Bayever disclosed active agents administered at 60 mg/m^2 (e.g. irinotecan) once per two weeks; Conroy disclosed oxaliplatin at 85 mg/m^2, as discussed above.

Claims 5-6 and 8 are rendered prima facie obvious because Bayever disclosed that 5-fluorouracil was administered intravenously over 46 hours, liposomal irinotecan was administered intravenously over 90 minutes, and that leucovorin was administered prior to 5-FU (page 12, section IV).

Claim 7 is rendered prima facie obvious because Bayever disclosed that active agents were administered on day one of a two week cycle, where cycles comprised at least one administration. For example, Bayever's method overlaps that which is instantly recited (e.g. administration on days 1 and 15 of a 28-day cycle) because administration on day 1 of at least one 2 week cycle can also be administration on days 1 and 15 of a 28 day cycle (e.g. two 2-week cycles). In the case where the claimed ranges "overlap or lie inside ranges disclosed by the prior art", a prima facie case of obviousness exists. MPEP 2144.05 A.

Claim 10 is rendered prima facie obvious because Bayever disclosed irinotecan sucrose octasulfate liposomal irinotecan, where the irinotecan is entrapped within the liposome, at page 4, and the last paragraph.

Applicant's Arguments and Examiner's Response

Applicants argued that the instant invention is different than the prior art because: Conroy disclosed 180 mg/m^2 irinotecan once every two weeks; Conroy did not disclose

liposomal irinotecan; Conroy disclosed 400 mg/m2 fluorouracil; Bayever disclosed 80 mg/m^2 liposomal irinotecan in combination with leucovorin and 5-fluorouracil.

The Examiner responds that Conroy was not relied upon to teach the claimed dosage and administration of liposomal irinotecan and fluorouracil, as Bayever disclosed said limitations. Further, the Examiner disagrees that Bayever disclosed 80 mg/m^2 liposomal irinotecan. Bayever disclosed 60 mg/m^2 liposomal irinotecan to patients homozygous for the UGT1A1 *28 allele, at page 3, embodiment (a).

Applicants argued that Bayever and Conroy do not provide guidance to an ordinarily skilled artisan to expect that oxaliplatin could alter deposition of irinotecan from liposomal irinotecan into human pancreatic tumors. Applicants argued that the prior art did not disclose that administering oxaliplatin in combination with liposomal irinotecan can initially reduce the irinotecan deposition into pancreatic cancers tumors in mouse xenograft studies, or that subsequently administering liposomal irinotecan after a sufficient interval can lead to an increase in irinotecan deposition in mouse xenograft models of pancreatic cancer.

The Examiner responds that the prior art was not relied upon to teach that oxaliplatin alters the deposition of irinotecan, as said limitation is not claimed.

Applicants argued that neither Bayever nor Conroy disclosed that an initial dose of oxaliplatin with liposomal irinotecan can unexpectedly decrease the deposition of irinotecan from liposomal irinotecan in pancreatic cancer tumors; that the subsequent administration of liposomal irinotecan after an effective interval unexpectedly leads to an increase in irinotecan deposition in the pancreatic cancer tumors.

The Examiner responds that the Applicants are encouraged to specifically point to evidence supporting conclusions of unexpectedness. The Applicants have the burden of proffering data and establishing results as unexpected and significant. Evidence of unexpected properties may be established by direct or indirect comparative tests. MPEP 716.02(b)(I)(II)(III).

Claims 4 and 9 are rejected under 35 U.S.C. 103 as being unpatentable over Bayever et al (WO 2013/188586), in view of Conroy et al (NEJM, 34(19), 2011, 1817) and further in view of Fleming et al (http://www.oncologynurseadvisor.com/advisor-forum/importance-of-sequence-in-chemotherapy-administration/article/378072/).

The 35 U.S.C. 103 rejection over Bayever, in view of Conroy has been discussed above.

Additionally, Conroy disclosed that a second active agent was given two hours after a first active agent (e.g. leucovorin was given two hours after oxaliplatin) (page 1819, 1st paragraph of the section entitled Treatment).

However, the combination of Bayever and Conroy did not specifically disclose oxaliplatin administration after liposomal irinotecan, as recited in claim 4; liposomal irinotecan administration, followed by oxaliplatin administration, followed by leucovorin administration, followed by 5-fluorouracil administration, as recited in claim 9.

Fleming disclosed that the sequence of various chemotherapy drugs in general does not matter, as the half-life of each drug makes it impossible to determine what

drug is at what level at any particular time, based on individual patient pharmacodynamics (last sentence of the first paragraph).

Since the combination of Bayever and Conroy disclosed administration of oxaliplatin, liposomal irinotecan, leucovorin and 5-fluorouracil, it would have been prima facie obvious to one of ordinary skill in the art to have varied the order of administration of the combined methods of Bayever and Conroy, such that the order of administration was liposomal irinotecan, followed by oxaliplatin, followed by leucovorin, followed by 5-fluorouracil administration. An ordinarily skilled artisan would have been motivated because the sequence of various chemotherapy drugs in general does not matter, as the half-life of each drug makes it impossible to determine what drug is at what level at any particular time, based on individual patient pharmacodynamics, as taught by Fleming (Fleming, last sentence of the first paragraph).

Applicant's Arguments and Examiner's Response

Applicants argued that claims 4 and 9 are patentable because claim 1 is patentable.

The Examiner responds that allowable subject matter has not been identified in claim 1.

Claims 11-15, 17 and 20 are rejected under 35 U.S.C. 103 as being unpatentable over Bayever et al (WO 2013/188586), in view of Conroy et al (NEJM, 34(19), 2011, 1817), as evidenced by Bayever et al (WO 2016/094402).

The 35 U.S.C. 103 rejection over Bayever (2013), in view of Conroy, has been discussed above.

Although, Bayever (2013) disclosed MM-398 liposome (at page 4, last paragraph and as discussed above), Bayever was not specific as to the ingredients of the liposome, as recited in claims 11-12, 17 and 20.

However, Bayever (2016) evidenced that MM-398 contained irinotecan sucrose octasulfate, DSPC, cholesterol and MPEG-2000-DSPE (page 30, section describing the drug product).

Thus, it is reasonable to assume that Bayever's (2013) MM-398 contains irinotecan, DSPC, cholesterol and MPEG-2000-DSPE, as evidenced by Bayever's (2016) disclosure of the liposomal constituents of MM-398.

Claims 13-15, 17 and 20 are rendered prima facie obvious because Bayever disclosed that 5-fluorouracil was administered intravenously over 46 hours, liposomal irinotecan was administered intravenously over 90 minutes; liposomal irinotecan was administered prior to leucovorin; leucovorin was administered prior to 5-FU (page 12, section IV). Further, Bayever disclosed that active agents were administered on day one of a two week cycle, where cycles comprised at least one administration. For example, Bayever's method overlaps that which is instantly recited (e.g. administration on days 1 and 15 of a 28-day cycle) because administration on day 1 of at least one 2 week cycle can also be administration on days 1 and 15 of a 28 day cycle (e.g. two 2-week cycles). A prima facie case of obviousness exists because of overlap, as discussed above.

Applicant's Arguments and Examiner's Response

Applicants argued that claims 11-15, 17 and 20 are patentable because claim 1 is patentable.

The Examiner responds that allowable subject matter has not been identified in claim 1.

Claim 18 is rejected under 35 U.S.C. 103 as being unpatentable over Bayever et al (WO 2013/188586), in view of Conroy et al (NEJM, 34(19), 2011, 1817) and further in view of Fleming et al (http://www.oncologynurseadvisor.com/advisor-forum/importance-of-sequence-in-chemotherapy-administration/article/378072/), as evidenced by Bayever et al (WO 2016/094402).

The 35 U.S.C. 103 rejection over Bayever, in view of Conroy as evidenced by Bayever has been discussed above.

Additionally, Bayever (2013) disclosed that prior to each administration of liposomal irinotecan, the patient was pre-medicated with dexamethasone (e.g. corticosteroid) and another anti-emetic (page 4, fourth embodiment from the top of the page).

Further, Conroy disclosed that a second active agent was given two hours after a first active agent (e.g. leucovorin was given two hours after oxaliplatin) (page 1819, 1st paragraph of the section entitled Treatment).

However, the combination of Bayever and Conroy did not specifically disclose liposomal irinotecan administration, followed by oxaliplatin administration, followed by leucovorin administration, followed by 5-fluorouracil administration, as recited in claim 18.

Fleming disclosed that the sequence of various chemotherapy drugs in general does not matter, as the half-life of each drug makes it impossible to determine what drug is at what level at any particular time, based on individual patient pharmacodynamics (last sentence of the first paragraph).

Since the combination of Bayever and Conroy disclosed administration of oxaliplatin, liposomal irinotecan, leucovorin and 5-fluorouracil, it would have been prima facie obvious to one of ordinary skill in the art to have varied the order of administration of the combined methods of Bayever and Conroy, such that the order of administration was liposomal irinotecan, followed by oxaliplatin, followed by leucovorin, followed by 5-fluorouracil administration. An ordinarily skilled artisan would have been motivated because the sequence of various chemotherapy drugs in general does not matter, as the half-life of each drug makes it impossible to determine what drug is at what level at any particular time, based on individual patient pharmacodynamics, as taught by Fleming (Fleming, last sentence of the first paragraph).

Applicant's Arguments and Examiner's Response

Applicants argued that claim 18 is patentable because claim 1 is patentable.

The Examiner responds that allowable subject matter has not been identified in claim 1.

Nonstatutory Double Patenting

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 1-20 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-4, 6-9 and 19-40 of copending Application No. 14/851,111, in view of Conroy et al (NEJM, 34(19), 2011, 1817).

Although the claims at issue are not identical, they are not patentably distinct from each other. The copending claims recite all of the features instantly recited for the antineoplastic therapy except for oxaliplatin. The instant claims require oxaliplatin, and such an ingredient is not recited by the copending claims. Also, the copending claims are further limited by the diameter of the liposomes.

Conroy disclosed FOLFIRINOX (oxaliplatin, 85 mg per square meter of body-surface area; irinotecan; leucovorin and fluorouracil) treatment of patients having metastatic pancreatic cancer (title and the methods section of the abstract). Conroy

disclosed that oxaliplatin has clinical activity against pancreatic cancer only when combined with fluorouracil, and that oxaliplatin and irinotecan have been shown to have synergistic activity in vitro (page 1818, left column, second paragraph).

Thus, it would have been obvious to have used oxaliplatin in the copending formulation, because oxaliplatin has clinical activity against pancreatic cancer when combined with fluorouracil, and because oxaliplatin and irinotecan have been shown to have synergistic activity in vitro.

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

Applicant's Arguments and Examiner's Response

The Applicants have not argued the obviousness-type nonstatutory double patenting rejection.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CELESTE A. RONEY whose telephone number is (571)272-5192. The examiner can normally be reached on Monday-Thursday; 7A-4P.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Fred Krass can be reached on 571-272-0580. 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.

/CELESTE A. RONEY/
Examiner, Art Unit 1612

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.
15/241,106	08/19/2016	Eliel Bayever	263266-411933	4520

139696 7590 07/10/2017

Honigman Miller Schwartz and Cohn LLP/Ipsen
350 East Michigan Avenue, Suite 300
Kalamazoo, MI 49007

EXAMINER
RONEY, CELESTE A

ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
07/10/2017	ELECTRONIC

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

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

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

patents@honigman.com
lzerby@honigman.com
anelson@honigman.com

Office Action Summary	Application No. 15/241,106	Applicant(s) BAYEVER ET AL.	
	Examiner CELESTE A. RONEY	Art Unit 1612	AIA (First Inventor to File) Status Yes

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

Period for Reply

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

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

Status

1)☒ Responsive to communication(s) filed on *3/29/17*.

☐ 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) *2,4-15 and 18-22* is/are pending in the application.

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

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *2,4-15,18-22* is/are rejected.

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

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* 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.

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

4) ☐ Other: _____.

DETAILED ACTION

Previous Rejections

Applicants' arguments, filed 3/29/17, have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 112 - Indefiniteness

The following is a quotation of 35 U.S.C. 112(b):
(b) CONCLUSION.—The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), second paragraph:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 14-15 and 21-22 are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention.

Claims 14-15 depend from a cancelled claim. In the interest of compact prosecution, claims 14-15 are interpreted as dependent from independent claim 19. However, appropriate correction is required.

Claims 21-22 recite a “dose level of -1.” It is unclear as to what a dose level of -1 refers. The Applicants are requested to clarify claim 21, regarding the reduced dosage,

since four individual antineoplastic ingredients are recited, and neither ingredient is further limited by the "-1". The Examiner notes that reciting the dosages of ingredients in claim 21, as they are recited in claim 19, would clarify the claim. Appropriate correction is required.

Claim Rejections - 35 USC § 103

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

> A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 2, 5-8, 10, 19 and 21-22 are rejected under 35 U.S.C. 103 as being unpatentable over Bayever et al (WO 2013/188586), in view of Conroy et al (NEJM, 34(19), 2011, 1817).

Bayever et al disclosed a method for treatment of pancreatic cancer in a patient (e.g., a human, at page 3, 1st paragraph), comprising co-administering to the patient active agents, at a dose of 60 mg/m^2 (e.g., liposomal irinotecan). Bayever further disclosed 5-fluorouracil at a dose of 2400 mg/m^2 and leucovorin (*l* form administered at 200 mg/m^2 or the *l+d* racemic form administered at 400 mg/m^2). The method comprised at least one cycle of administration, wherein the cycle was a period of two weeks (page 3, last full paragraph).

In one embodiment, Bayever's patient population was patients undergoing treatment for metastatic adenocarcinoma pancreatic cancer (e.g. a patient who has

not previously received an antineoplastic agent) (page 12, section V, last embodiment, and claim 10).

Bayever did not disclose oxaliplatin, as recited in claim 19.

Conroy disclosed FOLFIRINOX (oxaliplatin; irinotecan; leucovorin and fluorouracil) treatment of patients having metastatic pancreatic cancer (title and the methods section of the abstract). Conroy disclosed that oxaliplatin has clinical activity against pancreatic cancer only when combined with fluorouracil, and that oxaliplatin and irinotecan have been shown to have synergistic activity *in vitro* (page 1818, left column, second paragraph).

Conroy did not disclose that the irinotecan was liposomal irinotecan.

Since Bayever disclosed treating metastatic pancreatic carcinoma with 5-fluorouracil and irinotecan, it would have been prima facie obvious to one of ordinary skill in the art to have included oxaliplatin within Bayever's methods of treatment. An ordinarily skilled artisan would have been motivated because oxaliplatin has clinical activity against pancreatic cancer when combined with fluorouracil, and because oxaliplatin and irinotecan have synergistic activity *in vitro*, as taught by Conroy (Conroy, page 1818, left column, second paragraph).

The combination of Bayever and Conroy reads on claim 19.

Claim 2 is rendered prima facie obvious because Bayever disclosed active agents administered at 60 mg/m^2 (e.g. irinotecan) once per two weeks, as discussed above.

Claims 5-6 and 8 are rendered prima facie obvious because Bayever disclosed that 5-fluorouracil was administered intravenously over 46 hours, liposomal irinotecan was administered intravenously over 90 minutes, and that leucovorin was administered prior to 5-FU (page 12, section IV).

Claim 7 is rendered prima facie obvious because Bayever disclosed that active agents were administered on day one of a two week cycle, where cycles comprised at least one administration. For example, Bayever's method overlaps that which is instantly recited (e.g. administration on days 1 and 15 of a 28-day cycle) because administration on day 1 of at least one 2 week cycle can also be administration on days 1 and 15 of a 28 day cycle (e.g. two 2-week cycles). In the case where the claimed ranges "overlap or lie inside ranges disclosed by the prior art", a prima facie case of obviousness exists. MPEP 2144.05 A.

Claim 10 is rendered prima facie obvious because Bayever disclosed irinotecan sucrose octasulfate liposomal irinotecan, where the irinotecan was entrapped within the liposome, at page 4, and the last paragraph.

Claims 21-22 are rendered prima facie obvious because Bayever disclosed that the liposomal irinotecan may be initially administered at a high dose and may be lowered over time (e.g., reduced dosage), at page 13, last line; 5-FU may be initially administered at a high dose and may be lowered over time; leucovorin may be initially administered at a high dose and may be lowered over time (page 14, first two full paragraphs).

Applicant's Arguments and Examiner's Response

Applicants argued that neither Conroy nor Bayever discloses the claimed methods of treatment. Applicants argued that one of ordinary skill in the art would not have modified the teachings of Conroy and Bayever to arrive at the claimed methods of treatment with a reasonable expectation of success.

The Examiner disagrees that neither Bayever nor Conroy disclosed the claimed methods of treatment. Claim 19 recites administering once every two weeks: 60 mg/m^2 liposomal irinotecan; 60 mg/m^2 oxaliplatin; 400 mg/m^2 leucovorin and 2400 mg/m^2 5-FU. Bayever only differed from the instant claims by not disclosing the administration of oxaliplatin. However, Conroy disclosed oxaliplatin for the treatment of pancreatic cancer. The combination of Bayever and Conroy taught the claimed methods of treatment.

An ordinarily skilled artisan would have included Conroy's oxaliplatin within Bayever's treatment of pancreatic cancer protocol, with an expectation of success, because oxaliplatin has clinical activity against pancreatic cancer when combined with fluorouracil, and because oxaliplatin and irinotecan have synergistic activity *in vitro* (e.g., Bayever teaches fluorouracil and irinotecan treatment of pancreatic cancer), as taught by Conroy (Conroy, page 1818, left column, second paragraph).

Applicants argued that neither Conroy nor Bayever disclose or reasonably lead one of ordinary skill in the art to believe that there would be a change in plasma pharmacokinetic parameters between dose levels, as was found with the instant invention.

The Examiner responds that Bayever and Conroy were not relied upon to compare the results between dose levels, including the pharmacokinetic parameters between dose levels, as said limitations are not currently claimed.

Applicants argued that Bayever and Conroy do not provide guidance to an ordinarily skilled artisan to expect that oxaliplatin could alter deposition of irinotecan from liposomal irinotecan into human pancreatic tumors. Applicants argued that the prior art did not disclose that administering oxaliplatin in combination with liposomal irinotecan can initially reduce the irinotecan deposition into pancreatic tumors in mouse xenograft studies, or that subsequently administering liposomal irinotecan after a sufficient interval can lead to an increase in irinotecan deposition in mouse xenograft models of pancreatic cancer.

The Examiner responds that the prior art was not relied upon to teach that oxaliplatin alters the deposition of irinotecan, as said limitation is not claimed.

Applicants argued that, unexpectedly, Applicants are able to administer the dose level -1 to more patients with greater tolerability than the dose level 1. Applicants cited Example 4, and Tables 15 and 17 of the instant specification.

The Examiner disagrees that the Applicants have shown unexpected results regarding a greater tolerability of the administered formulation (e.g., a reduced dosage). Tables 15 and 17 appear to show the formulations, dosages and dose days. Tables 16 (seven patients) and 18 (five patients) appear to show the patients and the days/cycles on which the patients were treated.

As per Table 16, some patients received a reduced dosage, and some did not. There does not appear to be an indication as to how or why the patients receiving the reduced dosages were chosen. As per Table 18, showing 5 patients, only 1 patient received the reduced dosage. In summary, the data only appears to show that some patients received reduced dosages, and does not appear to show anything beyond the receipt of dosages. For example, the data does not appear to show tolerability.

Claims 4, 9 and 18 are rejected under 35 U.S.C. 103 as being unpatentable over Bayever et al (WO 2013/188586), in view of Conroy et al (NEJM, 34(19), 2011, 1817) and further in view of Fleming et al (http://www.oncologynurseadvisor.com/advisor-forum/importance-of-sequence-in-chemotherapy-administration/article/378072/).

The 35 U.S.C. 103 rejection over Bayever, in view of Conroy has been discussed above.

Additionally, Bayever disclosed that prior to each administration of liposomal irinotecan, the patient was pre-medicated with dexamethasone (e.g. corticosteroid) and another anti-emetic (page 4, fourth embodiment from the top of the page).

Further, Conroy disclosed that a second active agent was given two hours after a first active agent (e.g. leucovorin was given two hours after oxaliplatin) (page 1819, 1st paragraph of the section entitled Treatment).

However, the combination of Bayever and Conroy did not specifically disclose oxaliplatin administration after liposomal irinotecan, as recited in claims 4 and 18;

liposomal irinotecan administration, followed by oxaliplatin administration, followed by leucovorin administration, followed by 5-fluorouracil administration, as recited in claim 9.

Fleming disclosed that the sequence of various chemotherapy drugs in general does not matter, as the half-life of each drug makes it impossible to determine what drug is at what level at any particular time, based on individual patient pharmacodynamics (last sentence of the first paragraph).

Since the combination of Bayever and Conroy disclosed administration of oxaliplatin, liposomal irinotecan, leucovorin and 5-fluorouracil, it would have been prima facie obvious to one of ordinary skill in the art to have varied the order of administration of the combined methods of Bayever and Conroy, such that the order of administration was liposomal irinotecan, followed by oxaliplatin, followed by leucovorin, followed by 5-fluorouracil administration.

An ordinarily skilled artisan would have been motivated because the sequence of various chemotherapy drugs in general does not matter, as the half-life of each drug makes it impossible to determine what drug is at what level at any particular time, based on individual patient pharmacodynamics, as taught by Fleming (Fleming, last sentence of the first paragraph).

Applicant's Arguments and Examiner's Response

Applicants argued that claims 4 and 9 are patentable for at least the same reasons as is claim 19, as discussed above. Applicants argued that claim 18 depends from an allowable base claim and is patentable based on dependency.

The Examiner responds that claims 4, 9 and 18 are not patentable because patentable subject matter has not been identified in the instant application.

Claims 11-15 and 20 are rejected under 35 U.S.C. 103 as being unpatentable over Bayever et al (WO 2013/188586), in view of Conroy et al (NEJM, 34(19), 2011, 1817), as evidenced by Bayever et al (WO 2016/094402).

The 35 U.S.C. 103 rejection over Bayever (2013), in view of Conroy, has been discussed above.

Although, Bayever (2013) disclosed MM-398 liposome (at page 4, last paragraph and as discussed above), Bayever was not specific as to the ingredients of the liposome, as recited in claims 11-12 and 20.

However, Bayever (2016) evidenced that MM-398 contained irinotecan sucrose octasulfate, DSPC, cholesterol and MPEG-2000-DSPE (page 30, section describing the drug product).

Thus, it is reasonable to assume that Bayever's (2013) MM-398 contained irinotecan, DSPC, cholesterol and MPEG-2000-DSPE, as evidenced by Bayever's (2016) disclosure of the liposomal constituents of MM-398.

Claims 13-15 and 20 are rendered prima facie obvious because Bayever disclosed that 5-fluorouracil was administered intravenously over 46 hours, liposomal irinotecan was administered intravenously over 90 minutes; liposomal irinotecan was administered prior to leucovorin; leucovorin was administered prior to 5-FU (page 12, section IV). Further, Bayever disclosed that active agents were

administered on day one of a two week cycle, where cycles comprised at least one administration.

For example, Bayever's method overlaps that which is instantly recited (e.g. administration on days 1 and 15 of a 28-day cycle) because administration on day 1 of at least one 2 week cycle can also be administration on days 1 and 15 of a 28 day cycle (e.g. two 2-week cycles). A prima facie case of obviousness exists because of overlap, as discussed above.

Applicant's Arguments and Examiner's Response

Applicants argued that claims 11-15 and 20 are patentable for at least the same reasons as is claim 19, as discussed above.

The Examiner responds that claims 11-15 and 20 are not patentable because patentable subject matter has not been identified in the instant application.

Nonstatutory Double Patenting

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 2, 4-15 and 18-22 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-30 of U.S. Patent No. 9,492,442, in view of Conroy et al (NEJM, 34(19), 2011, 1817).

Although the claims at issue are not identical, they are not patentably distinct from each other. The issued claims recite all of the features instantly recited for the antineoplastic therapy except for oxaliplatin. The instant claims require oxaliplatin, and such an ingredient is not recited by the issued claims. Also, the issued claims are further limited by the diameter of the liposomes.

Conroy disclosed FOLFIRINOX (oxaliplatin, 85 mg per square meter of body-surface area; irinotecan; leucovorin and fluorouracil) treatment of patients having metastatic pancreatic cancer (title and the methods section of the abstract). Conroy disclosed that oxaliplatin has clinical activity against pancreatic cancer only when combined with fluorouracil, and that oxaliplatin and irinotecan have been shown to have synergistic activity in vitro (page 1818, left column, second paragraph).

Thus, it would have been obvious to have used oxaliplatin in the issued formulation, because oxaliplatin has clinical activity against pancreatic cancer when combined with fluorouracil, and because oxaliplatin and irinotecan have been shown to have synergistic activity *in vitro*.

Applicant's Arguments and Examiner's Response

Applicants argued that if pending claims are found to be allowable, then the Applicants will submit a terminal disclaimer along with the required fee, thereby obviating the double patenting rejection.

The Examiner responds that patentable subject matter has not been identified in the instant application, and as such, the obvious type nonstatutory double patenting rejection is maintained.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CELESTE A. RONEY whose telephone number is (571)272-5192. The examiner can normally be reached on Monday-Thursday; 7A-5P.

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, Fred Krass can be reached on 571-272-0580. 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.

/CELESTE A. RONEY/
Examiner, Art Unit 1612

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/241,128	08/19/2016	ELIEL BAYEVER	239669-401502/100.1056US0	7490

133156 7590 11/25/2016

Honigman Miller Schwartz and Cohn LLP
350 East Michigan Avenue
Suite 300
Kalamazoo, MI 49007

EXAMINER
STRONG, TORI

ART UNIT	PAPER NUMBER
1629	

NOTIFICATION DATE	DELIVERY MODE
11/25/2016	ELECTRONIC

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

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

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

patents@honigman.com
arhoades@honigman.com

Office Action Summary	Application No. 15/241,128	Applicant(s) BAYEVER ET AL.	
	Examiner TORI M. STRONG	Art Unit 1629	AIA (First Inventor to File) Status Yes

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

Period for Reply

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

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

Status

1)☒ Responsive to communication(s) filed on *19 August 2016*.

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

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

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; 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) *1-20* is/are pending in the application.

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

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-20* 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 *16 September 2016* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

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

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

Priority under 35 U.S.C. § 119

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

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

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

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

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

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

Attachment(s)

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

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

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

4) ☐ Other: _____.

DETAILED ACTION

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.

Status of Claims

Claims 1-20 are pending in the instant application and are the subject of the Office Action below.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on October 31, 2016 was filed after the mailing date of the application on August 19, 2016. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner. Enclosed with this Office Action are return copies of Form PTO/SB/08B with the Examiner's initials and signature indicating those references that have been considered.

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 1-20 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-27 of U.S. Patent No. 9,339,497 B2; claims 1-29 of U.S. Patent No. 9,364,473 B2; claims 1-35 of U.S. Patent No. 9,452,162 B2; and claims 1-30 of U.S. Patent No. 9,492,442 B2. Although the claims at issue are not identical, they are not patentably distinct from each other because each disclosure sets out to claim treatment of pancreatic cancer with the antiproliferative therapeutic regimen that consist of liposomal irinotecan at a dosing of 60, 70 or 80 mg/m^2; leucovorin (*l*-form) at a dose if 200 mg/m^2; and 5-fluorouracil at a dose of 2,400 mg/m^2. Each disclosure teaches and claims treating patients refractory to gemcitabine therapy and treating patients who either are or not homozygous for the UGT1A1*28 allele. The closest prior art, as indicated in the record of previous case App. No. 14/812,950 (now patented U.S. Patent No. 9,339,497 B2) is found in Yoo *et al.* (*British Journal of Cancer*, 2009, 101, pp. 1658-163); where Yoo teaches treating pancreatic cancer refractory to gemcitabine therapy with the mFOIRIRI.3 regimen that consists of irinotecan, leucovorin and 5-fluorouracil. However, Yoo requires different dosing and that irinotecan is administered twice where the therapy provides the overall survival for the mFOIRIRI.3 regimen to be

16.6 weeks (or 4.2 months). The instantly claimed invention carves out a specific regimen that requires the dosing of the components and administers the drugs only once within a cycle and further provides for the unexpected result of improving clinical benefit of up to 80% and the increasing the patient population survival of at least 6 months. Therefore the claims are free of the art. However, the claims are obvious variants of the previously patented subject matter and therefore the nonstatutory double patenting rejection is applied.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TORI M. STRONG whose telephone number is (571)272-6333. The examiner can normally be reached on Monday-Friday 8am-5pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Lundgren can be reached on 571-272-5541. 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.

/TORI M STRONG/
Examiner, Art Unit 1629

/Kortney L. Klinkel/
Primary Examiner, Art Unit 1611

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/296,536	10/18/2016	DARYL C. DRUMMOND	239669-403892/1001130US17	1088

133156 7590 03/08/2017

Honigman Miller Schwartz and Cohn LLP
350 East Michigan Avenue
Suite 300
Kalamazoo, MI 49007

EXAMINER
KISHORE, GOLLAMUDI S

ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
03/08/2017	ELECTRONIC

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

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

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

patents@honigman.com
lbroecker@honigman.com
lzerby@honigman.com

Office Action Summary	Application No. 15/296,536	Applicant(s) DRUMMOND ET AL.	
	Examiner Gollamudi S. Kishore, PhD	Art Unit 1612	AIA (First Inventor to File) Status No

-- 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 _____.

☐ 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* is/are pending in the application.

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

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1* 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 _____ 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: _____.

DETAILED ACTION

Claim included in the prosecution is claim 1.

Double Patenting

1. 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.

2. Claim 1 is rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-35 of U.S. Patent No. 8,147,867. Although the claims at issue are not identical, they are not patentably distinct from each other because the instant claim is drawn to a liposomal formulation containing irinotecan and sucrose octasulfate and liposomes contain DSPC, cholesterol and PEG_DSPE in specific molar ratios and the patented claims are drawn to the same liposomal compositions containing irinotecan and sucrose octasulfate. The dependent claims recite DSPC and PEG_DSPE. The patented claim 1 is generic with respect to the ratios in instant claim 1 and therefore, includes instant specific ratios and thus, an obvious variant of the patented claims.

3. Claim 1 is rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-22 of U.S. Patent No. 8,658,203. Although the claims at issue are not identical, they are not patentably distinct from each other because the patented claims are drawn to a method of treating brain tumor using a liposomal composition containing irinotecan and sucrose octasulfate; the patented claims are generic with respect to the amounts of irinotecan and the components making up the liposomes and their ratios. Instant claim is drawn to a liposomal formulation containing irinotecan and sucrose octasulfate and liposomes contain DSPC, cholesterol and PEG_DSPE in specific molar ratios. The patented generic claims thus, encompass instant specific components and ratios. Although the patented claims are drawn to a method of treating brain tumor since there was no restriction made in the parent case, the instant composition claim is still deemed obvious over the patented method claim using the same claimed composition.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gollamudi S. Kishore, PhD whose telephone number is (571)272-0598. The examiner can normally be reached on 6:30 AM- 4 PM, alternate Friday off.

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, Krass Frederick can be reached on (571) 272-0580. 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.

/Gollamudi S. Kishore/
Primary Examiner, Art Unit 1612

GSK

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/331,393	10/21/2016	Daryl C. Drummond	239669-403893	6925

133156 7590 01/19/2017

Honigman Miller Schwartz and Cohn LLP
350 East Michigan Avenue
Suite 300
Kalamazoo, MI 49007

EXAMINER	
SHOMER, ISAAC	

ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
01/19/2017	ELECTRONIC

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

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

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

patents@honigman.com
lbroecker@honigman.com
lzerby@honigman.com

Notice of References Cited	Application/Control No. 15/331,393	Applicant(s)/Patent Under Reexamination DRUMMOND ET AL.	
	Examiner ISAAC SHOMER	Art Unit 1612	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	CPC Classification	US Classification
*	A	US-2007/0110798 A1	05-2007	Drummond; Daryl C.	A61K9/0019	424/450
*	B	US-2007/0116753 A1	05-2007	Hong; Keelung	A61K9/0019	424/450
*	C	US-8,147,867 B2	04-2012	Hong; Keelung	A61K9/0019	424/450
*	D	US-8,329,213 B2	12-2012	Hong; Keelung	A61K9/0019	424/450
*	E	US-8,658,203 B2	02-2014	Drummond; Daryl C.	A61K9/0019	424/450
*	F	US-8,703,181 B2	04-2014	Hong; Keelung	A61K9/0019	424/450
*	G	US-8,992,970 B2	03-2015	Hong; Keelung	A61K9/0019	424/417
	H	US-				
	I	US-				
	J	US-				
	K	US-				
	L	US-				
	M	US-				

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	CPC Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

First Action Interview Pilot Program Pre-Interview Communication	Application No. 15/331,393	Applicant(s) DRUMMOND ET AL.	
	Examiner ISAAC SHOMER	Art Unit 1612	AIA (First Inventor to File) Status Yes

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

THE SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE **ONE MONTH OR THIRTY (30) DAYS,** WHICHEVER IS LONGER, FROM THE MAILING OR NOTIFICATION DATE OF THIS COMMUNICATION.

This time period for reply is extendable under 37 CFR 1.136(a) for only ONE additional MONTH.

This communication constitutes notice under 37 CFR 1.136(a)(1)(i).

Applicant must, within the time period for reply, file: (1) A letter requesting not to have a first action interview; (2) A reply under 37 CFR 1.111 waiving the first action interview and First Action Interview Office Action; or (3) An Applicant Initiated Interview Request Form (PTOL-413A) electronically via EFS-Web, accompanied by a proposed amendment or arguments, and schedule the interview within 2 months from the filing of the request. A failure to respond to this communication will be treated as a request not to have an interview. If applicant waives the First Action Interview Office Action, the instant Pre-Interview Communication is deemed the first Office Action on the Merits. The next subsequent Office action may be made final if appropriate. See MPEP 706.07(a).

Status

1)☒ Responsive to communication(s) filed on *21 October 2016*.

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

Disposition of Claims

2)☒ Claim(s) *1-20* is/are pending in the application.

2a) Of the above claim(s) _____ is/are withdrawn from consideration.

3)☐ Claim(s) _____ is/are allowed.

4)☒ Claim(s) ***1-20*** is/are rejected.

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

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

Application Papers

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

8)☐ 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

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

a)☐ All b)☐ Some * c)☐ None of:

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.

Contact Information

Examiner's Telephone Number: (571)270-7671

Examiner's Typical Work Schedule: 8:00 AM - 5:00 PM Monday-Friday

Supervisor's Name: Frederick F. Krass

Supervisor's Telephone Number:

Attachment(s)

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

2) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.

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

4) ☐ Other: _____.

First Action Interview Pilot Program Pre-Interview Communication	**Application No.** 15/331,393	**Applicant(s)** DRUMMOND ET AL.	
	Examiner ISAAC SHOMER	**Art Unit** 1612	**AIA (First Inventor to File) Status** Yes

Notification of Rejection(s) and/or Objection(s)

#	Claim(s)	Reference(s) (if applicable)	Rejection Statutory Basis	Brief Explanation of Rejection
1	1-20	US 2007/0116753 A1	102(a)(1)/103	Liposome comprising irinotecan (CPT-11) and sucrose octasulfate in at least Examples 73 and 74 on page 46. The examiner notes that the publication date of this reference is at least over a year prior to the instant effective filing date. See below for more info.
2	1-20	US 2007/0110798 A1	102(a)(1)/103	Liposome comprising irinotecan (CPT-11) and sucrose octasulfate in at least pages 28-31 Examples 13-17. The examiner notes that the publication date of this reference is at least over a year prior to the instant effective filing date. See below for more info.
3	1-20	15/331,648	Double Patenting	The product made by the method of the copending claims appears to be within the scope of the instant claims.

Expanded Discussion/Commentary

1		See page 46, Examples 73 and 74 of reference for liposome with irinotecan (CPT-11) and sucrose octasulfate. Liposome lipids include DSPC, cholesterol, and DSPE-PEG, paragraph [0108]. Weight ratio of drug/lipid in [0107], also citing example 74. Liposome size of 110-120 nm on [0124] and Table 38. Other parameters either anticipated in view of inherency or prima facie obvious based upon range overlap or optimization.
2		See pages 28-31, Examples 13-17 for liposomes comprising irinotecan (CPT-11) and sucrose octasulfate. Liposome lipids include DSPC, cholesterol, and DSPE-PEG, as of [0116]. Weight ratio in paragraph [0115]. Liposome size of 50-150 nm in [0145] and page 28 Table 9. Other parameters either anticipated in view of inherency or prima facie obvious based upon range overlap or optimization.
		The examiner additionally notes that there are a large number of references that have essentially the same disclosure as references #1 and #2 cited above as they are part of the priority series that includes the cited references. Relevant references are cited on the PTO-892.
		Relevant patents include 8147867, 8329213, 8703181, 8992970, 8658203. Relevant US serial numbers include but may not limited to 14/965140, 14/632422, 15/213127, 14/879302, 14/966458, 14/181583, 15/227631, 15/227561, and 15/296536. The issues relating to these cases are essentially the same as the issues relating to #1 and #2 above.

DATE:	/ISAAC SHOMER/ Primary Examiner, Art Unit 1612	

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/331,393	10/21/2016	Daryl C. Drummond	239669-403893/1088US02	6925

133156 7590 03/20/2017

Honigman Miller Schwartz and Cohn LLP
350 East Michigan Avenue
Suite 300
Kalamazoo, MI 49007

EXAMINER	
SHOMER, ISAAC	

ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
03/20/2017	ELECTRONIC

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

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

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

patents@honigman.com
lbroecker@honigman.com
lzerby@honigman.com

Applicant-Initiated Interview Summary	Application No.	Applicant(s)		
	15/331,393	DRUMMOND ET AL.		
	Examiner	Art Unit	AIA (First Inventor to File) Status	Page
	ISAAC SHOMER	1612	Yes	1 of 2

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

1. ISAAC SHOMER (Primary Examiner); Telephonic
2. Meghan Klaric (Attorney of Record); Telephonic
3. Nick Bolvin (Attorney); Telephonic
4. Heidi Berven (Attorney); Telephonic

Date of Interview: 13 March 2017

Claim(s) discussed: 21 (proposed claim)

Identification of prior art discussed: US 2007/0110798 A1 (of record)

US 2007/0116753 A1 (of record)

M Grit, JH de Smidt, A Struijke, DJA Crommelin. "Hydrolysis of Phosphatidylcholine in Aqueous Liposome Dispersions." International Journal of Pharmaceutics, Vol. 50, 1989, pages 1-6.

M Grit, WJM Underberg, DJA Crommelin. "Hydrolysis of Saturated Soybean Phosphatidylcholine in Aqueous Liposome Dispersions." Journal of Pharmaceutical Sciences, Vol. 82 No. 4, April 1993, pages 362-366.

AM Saetern, M Skar, A Braaten, M Brandl. "Camptothecin-catalyzed phospholipid hydrolysis in liposomes." International Journal of Pharmaceutics, Vol. 288, 2005, pages 73-80.

Brief Description of main topic of discussion: Representatives of applicant explained how the claimed invention has greater storage stability than the compositions of the prior art.

Issues Discussed:

Item(s) under 35 U.S.C. 112:
Examiner expressed concern about applicant's propsal to provide new claim 21 with a gram-equivalent ratio of 0.994 to 1.049, the concern being that this is new matter. In response, representative of applicant expressed the position that amended claims will be filed with new lower and upper limits that are clearly supported. The examiner also requested that applicant calculate the gram-equivalent ratio of a prior art example, as this may be an area of difference between the claimed invention and the prior art.

Nature of Invention and state of art:
This interview was conducted as part of the first action interview pilot program. Prior to discussing the difference between the prior art and the instantly claimed invention, representative of applicant discussed the state of the art regarding irinotecan containing liposomes. Representative of applicant explained that liposomes, especially those containing camptothecin or derivatives thereof as the active agent (of which irinotecan is a camptothecin derivative) have a problem with degradation in storage. While such a liposome can be prepared, such liposomal preparations will degrade when stored for multiple months in the refrigerator.
Representative of applicant explained that the problem with such liposomes in the prior art is that the phosphatidylcholine, which is a phospholipid with two alkyl chains, degrades to lysophosphatidylcholine, which is a phospholipid with one alkyl chain. This phospholipid subsequently leaves the liposome, resulting in drug leakage from the liposome.
Representative of applicant explained that the instant invention set out to solve the problem of such drug leakage.
Representative of applicant also cited three references drawn to the state of the art; two references by Grit et al. and one reference by Sattern et al. Representative of applicant explained that these references teach that liposomal phosphatidylcholine is the most stable to degradation to lysophosphatidylcholine at a pH of about 6.25-6.5. Representative of applicant also cited Sattern as teaching that a camptothecin liposome has inadequate storage stability for a marketable pharmaceutica lproduct, citing page 79, right column, bottom paragraph.

Evidence of Non-Obviousness:
Representative of applicant explained that although both the claimed invention and prior art are drawn to sucrose octasulfate containing irinotecan liposomes, the primary differences between the claimed invention and the prior art is the following. The instantly claimed liposome (as of the proposed claim) is stored in a medium wherein the pH is 7.25 to 7.50. Representative of applicant explained that the prior art suggests storing the liposomes in a medium of a pH of about 6.5 to minimize degradation of phosphatidylcholine to lysophosphatidylcholine, and cited additional prior art references to show that the prior art recognizes that a pH of 6.5 is optimum for minimizing degradation. However, representative of applicant cited Table 1 on pages 22 and 23 of the instant specification as showing that a pH value of 7.5 appears to

result in less degradation to lysophosphatidylcholine than a pH value of 6.5. Examiner agreed that applicant has shown unexpected results with respect to the pH. The examiner notes that the improved stability was primarily determined by the Mol Lyso-PC column of the table, with a lower mol% resulting in higher stability.

Other:
In view of the remaining issue regarding gram-equivalent ratio, the proposed amendments on 02/19/2017 are not entered as part of the first action interview pilot program. Applicant will submit a new amendment that incorporates the issues discussed in this interview.

Attachment(s): Other, PTO-892 with references; PTO-413FA (FAI Step 2)

/ISAAC SHOMER/ Primary Examiner, Art Unit 1612	

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

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

Applicant is reminded that a complete written statement as to the substance of the interview must be made of record in the application file. It is the applicant's responsibility to provide the written statement, unless the interview was initiated by the Examiner and the Examiner has indicated that a written summary will be provided. See MPEP 713.04

Please further see:

MPEP 713.04
Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews, paragraph (b)
37 CFR § 1.2 Business to be transacted in writing

First Action Interview Office Action Summary	Application No. 15/331,393	Applicant(s) DRUMMOND ET AL.	
	Examiner ISAAC SHOMER	Art Unit 1612	AIA (First Inventor to File) Status Yes

The MAILING OR NOTIFICATION DATE of this communication appears on the cover sheet with the correspondence address.

THE SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE **TWO MONTHS** FROM THE MAILING OR NOTIFICATION DATE OF THIS COMMUNICATION.

This time period for reply is extendable under 37 CFR 1.136(a) for only TWO additional MONTHS.

☐ Applicant's request to not have a first-action interview is acknowledged (or the time period for reply set forth in the Pre-Interview Communication has expired and the Office did not receive any reply).

Status

1) ☒ Responsive to communication(s) filed on *19 February 2017* and interview conducted on *10 March 2017*.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.
2) ☐ 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

3) ☒ Claim(s) *1-20* is/are pending in the application.
   3a) Of the above claim(s) _____ is/are withdrawn from consideration.
4) ☐ Claim(s) _____ is/are allowed.
5) ☒ Claim(s) *1-20* is/are rejected.
6) ☐ Claim(s) _____ is/are objected to.
7) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

8) ☐ The specification is objected to by the Examiner.
9) ☐ 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

10) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some * c) ☐ None of:
   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.

Contact Information

Examiner's Telephone Number: (571)270-7671

Examiner's Typical Work Schedule: 8:00 AM - 5:00 PM Monday-Friday

Supervisor's Name: Frederick F. Krass

Supervisor's Telephone Number: 571-272-0580

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: _____.

First Action Interview Office Action Summary	Application No. 15/331,393	Applicant(s) DRUMMOND ET AL.	
	Examiner ISAAC SHOMER	Art Unit 1612	AIA (First Inventor to File) Status No

Notification of Rejection(s) and/or Objection(s)

#	Claim(s)	Reference(s) (if applicable)	Rejection Statutory Basis	Brief Explanation of Rejection
1	1-20	US 2007/0116753 A1	102(a)(1)/103	Liposome comprising irinotecan (CRT-11) and sucrose octasulfate in at least Examples 73 and 74 on page 46. The examiner notes that the publication date of this reference is at least over a year prior to the instant effective filing date. See below for more info
2	1-20	US 2007/0110798 A1	102(a)(1)/103	Liposome comprising irinotecan (CRT-11) and sucrose octasulfate in at least pages 28-31 Examples 13-17. The examiner notes that the publication date of this reference is at least over a year prior to the instant effective filing date. See below for more info.

Expanded Discussion/Commentary

1		See page 46, Examples 73 and 74 of reference for liposome with irinotecan (CRT-11) and sucrose octasulfate. Liposome lipids include DSPC, cholesterol, and DSPE-PEG, paragraph [0108], Weight ratio of drug/lipid in [0107], also citing example 74. Liposome size of 110-120 nm on [0124] and Table 38. Other parameters either anticipated in view of inherency or prima facie obvious based upon range overlap or optimization.
2		See pages 28-31, Examples 13-17 for liposomes comprising irinotecan (CRT-11) and sucrose octasulfate. Liposome lipids include DSPC, cholesterol, and DSPE-PEG, as of [0116], Weight ratio in paragraph [0115], Liposome size of 50-150 nm in [0145] and page 28 Table 9. Other parameters either anticipated in view of inherency or prima facie obvious based upon range overlap or optimization.
		The examiner additionally notes that there are a large number of references that have essentially the same disclosure as references #1 and #2 cited above as they are part of the priority series that includes the cited references.
		Relevant patents include 8147867, 8329213, 8703181,8992970, 8658203. Relevant US serial numbers include but may not limited to 14/965140, 14/632422, 15/213127, 14/879302, 14/966458, 14/181583, 15/227631,15/227561, and 15/296536. The issues relating to these cases are essentially the same as the issues relating to #1 and #2 above.

DATE:	/ISAAC SHOMER/ Primary Examiner, Art Unit 1612	

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Alexandria, Virginia 22313-1450
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/331,648	10/21/2016	Daryl C. Drummond	239669-403110	4144

133156 7590 01/19/2017

Honigman Miller Schwartz and Cohn LLP
350 East Michigan Avenue
Suite 300
Kalamazoo, MI 49007

EXAMINER	
SHOMER, ISAAC	

ART UNIT	PAPER NUMBER
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NOTIFICATION DATE	DELIVERY MODE
01/19/2017	ELECTRONIC

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patents@honigman.com
lbroecker@honigman.com
lzerby@honigman.com

Notice of References Cited	Application/Control No. 15/331,648	Applicant(s)/Patent Under Reexamination DRUMMOND ET AL.	
	Examiner ISAAC SHOMER	Art Unit 1612	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	CPC Classification	US Classification
*	A	US-2007/0110798 A1	05-2007	Drummond; Daryl C.	A61K9/0019	424/450
*	B	US-2007/0116753 A1	05-2007	Hong; Keelung	A61K9/0019	424/450
*	C	US-8,147,867 B2	04-2012	Hong; Keelung	A61K9/0019	424/450
*	D	US-8,329,213 B2	12-2012	Hong; Keelung	A61K9/0019	424/450
*	E	US-8,658,203 B2	02-2014	Drummond; Daryl C.	A61K9/0019	424/450
*	F	US-8,703,181 B2	04-2014	Hong; Keelung	A61K9/0019	424/450
*	G	US-8,992,970 B2	03-2015	Hong; Keelung	A61K9/0019	424/417
	H	US-				
	I	US-				
	J	US-				
	K	US-				
	L	US-				
	M	US-				

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	CPC Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

First Action Interview Pilot Program Pre-Interview Communication	Application No. 15/331,648	Applicant(s) DRUMMOND ET AL.	
	Examiner ISAAC SHOMER	Art Unit 1612	AIA (First Inventor to File) Status Yes

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

THE SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE **ONE MONTH OR THIRTY (30) DAYS,** WHICHEVER IS LONGER, FROM THE MAILING OR NOTIFICATION DATE OF THIS COMMUNICATION.

This time period for reply is extendable under 37 CFR 1.136(a) for only ONE additional MONTH.

This communication constitutes notice under 37 CFR 1.136(a)(1)(i).

Applicant must, within the time period for reply, file: (1) A letter requesting not to have a first action interview; (2) A reply under 37 CFR 1.111 waiving the first action interview and First Action Interview Office Action; or (3) An Applicant Initiated Interview Request Form (PTOL-413A) electronically via EFS-Web, accompanied by a proposed amendment or arguments, and schedule the interview within 2 months from the filing of the request. A failure to respond to this communication will be treated as a request not to have an interview. If applicant waives the First Action Interview Office Action, the instant Pre-Interview Communication is deemed the first Office Action on the Merits. The next subsequent Office action may be made final if appropriate. See MPEP 706.07(a).

Status

1)☒ Responsive to communication(s) filed on *21 October 2016*.

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

Disposition of Claims

2)☒ Claim(s) *1-20* is/are pending in the application.

2a) Of the above claim(s) _____ is/are withdrawn from consideration.

3)☐ Claim(s) _____ is/are allowed.

4)☒ Claim(s) *1-20* is/are rejected.

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

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

Application Papers

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

8)☐ 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

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

a)☐ All b)☐ Some * c)☐ None of:

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.

Contact Information

Examiner's Telephone Number: (571)270-7671

Examiner's Typical Work Schedule: 8:00 AM - 5:00 PM Monday-Friday

Supervisor's Name: Frederick F. Krass

Supervisor's Telephone Number:

Attachment(s)

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

2) ☒Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.

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

4) ☐ Other: _____.

First Action Interview Pilot Program Pre-Interview Communication	Application No. 15/331,648	Applicant(s) DRUMMOND ET AL.	
	Examiner ISAAC SHOMER	Art Unit 1612	AIA (First Inventor to File) Status No

Notification of Rejection(s) and/or Objection(s)

#	Claim(s)	Reference(s) (if applicable)	Rejection Statutory Basis	Brief Explanation of Rejection
1	1-20	US 20070116753 A1	102(a)(1)/103	Liposome comprising irinotecan (CPT-11) in triethylammonium sucrose octasulfate taught as of page 46, Example 73. Examiner notes that reference was published over a year prior to instant filing date. See additional information below.
2	1-20	US 20070010798 A1	102(a)(1)/103	Liposome comprising irinotecan (CPT-11) in triethylammonium sucrose octasulfate taught on page 26, Example 11. Example 73. Examiner notes that reference was published over a year prior to instant filing date. See additional information below.

Expanded Discussion/Commentary

1		Liposome with phospholipid, triethylammonium sucrose octasulfate, and irinotecan (CPT-11) at page 46, Example 73. Weight ratio in paragraph 0107. Lipids in paragraph 0108. Storage stability at least in paragraph 0112. Even if, purely en arguendo, the preparation process is different in prior art as compared to claimed process, this does not necessarily overcome rejection - see MPEP 2113. Additional numerical parameters appear either anticipated by inherency or obviousness via range overlap and optimization.
2		Liposome with phospholipid, triethylammonium sucrose octasulfate, and irinotecan at page 26 Example 11. Weight ratio in paragraph 0115. Lipids in paragraph 0116. Storage stability in paragraph 0125. Even if, purely en arguendo, the preparation process is different in prior art as compared to claimed process, this does not necessarily overcome rejection - see MPEP 2113. Additional numerical parameters appear either anticipated by inherency or obviousness via range overlap and optimization.
		The examiner notes that there are additional documents which have the same subject matter documents #1 and #2 cited above. US Patents include 8147867, 8329213, 8703181, 8992970, and 8,658,203. US application numbers include 14/965140, 14/632422, 15/213127, 14/879302, 14/966458, 14/181583, 15/227631, 15/227561, 15/296536.
		It is the examiner's position with the above-cited patents and US serial numbers, the reasons for rejection are essentially the same as those for documents #1 and #2 above as these documents have essentially the same disclosure as documents #1 and #2.

DATE:	/ISAAC SHOMER/ Primary Examiner, Art Unit 1612	

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/331,648	10/21/2016	Daryl C. Drummond	239669-403110/1088US01	4144

133156 7590 03/17/2017

Honigman Miller Schwartz and Cohn LLP
350 East Michigan Avenue
Suite 300
Kalamazoo, MI 49007

EXAMINER	
SHOMER, ISAAC	

ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
03/17/2017	ELECTRONIC

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

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

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

patents@honigman.com
lbroecker@honigman.com
lzerby@honigman.com

Applicant-Initiated Interview Summary	Application No.	Applicant(s)		
	15/331,648	DRUMMOND ET AL.		
	Examiner	Art Unit	AIA (First Inventor to File) Status	Page
	ISAAC SHOMER	1612	Yes	1 of 2

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

1. ISAAC SHOMER (Primary Examiner); Telephonic
2. Meghan Klaric (Attorney of Record); Telephonic
3. Nick Bolvin (Attorney); Telephonic
4. Heidi Berven (Attorney); Telephonic

Date of Interview: 13 March 2017

Claim(s) discussed: 21

Identification of prior art discussed: US 2007/0110798 A1 (of record)
US 2007/0116753 A1 (of record)
M Grit, JH de Smidt, A Struijke, DJA Crommelin. "Hydrolysis of Phosphatidylcholine in Aqueous Liposome Dispersions." International Journal of Pharmaceutics, Vol. 50, 1989, pages 1-6.
M Grit, WJM Underberg, DJA Crommelin. "Hydrolysis of Saturated Soybean Phosphatidylcholine in Aqueous Liposome Dispersions." Journal of Pharmaceutical Sciences, Vol. 82 No. 4, April 1993, pages 362-366.
AM Saetern, M Skar, A Braaten, M Brandl. "Camptothecin-catalyzed phospholipid hydrolysis in liposomes." International Journal of Pharmaceutics, Vol. 288, 2005, pages 73-80.

Brief Description of main topic of discussion: Representatives of applicant explained how the claimed invention has greater storage stability than the compositions of the prior art.

Issues Discussed:

Item(s) under 35 U.S.C. 103:
Representative of applicant explained that although both the claimed invention and prior art are drawn to sucrose octasulfate containing irinotecan liposomes, the primary differences between the claimed invention and the prior art are the following:

A) First, the instantly claimed liposome is stored in a medium wherein the pH is 7.25 to 7.50. Representative of applicant explained that the prior art suggests storing the liposomes in a medium of a pH of about 6.5 to minimize degradation of phosphatidylcholine to lysophosphatidylcholine, and cited additional prior art references to show that the prior art recognizes a pH of 6.5 to be the optimum pH for minimizing degradation. However, representative of applicant cited table 1 on pages 22 and 23 of the instant specification as showing that a pH value of 7.25 to 7.5 appears to result in less degradation to lysophosphatidylcholine than a pH value of 6.5. Examiner agreed that applicant has shown unexpected results with respect to the pH. The examiner notes that the improved stability was primarily determined by the Mol Lyso-PC column of the table, with a lower mol% resulting in higher stability.

2) Representative of applicant explained that in the instantly claimed product-by-process, loading of sucrose octasulfate between 0.450 to 0.475 M was used, whereas in the examples of the prior art, the concentration of sucrose octasulfate was at minimum 0.65 M. Representative of applicant again cited Table 1 on pages 22 and 23 of the instant specification as showing unexpected results in improved stability at the lower concentration. Examiner agreed with this position. The examiner again notes that the improved stability was primarily determined by the Mol Lyso-PC column of the table, with a lower mol% resulting in higher stability. The examiner also pointed out that the data may show that the use of 0.450-0.475 M sucrose octasulfate may have resulted in the same amount of irinotecan being loaded as compared with 0.65 M sucrose octasulfate; this would have also been unexpected because the skilled artisan would have expected lower loading of irinotecan upon reducing the sucrose octasulfate concentration.

As such, the examiner agrees that the instantly claimed invention is not obvious over US 2007/0116753 A1 and 2007/0110798 A1.

Nature of Invention and state of art:
This interview was conducted as part of the first action interview pilot program. Prior to discussing the difference between the prior art and the instantly claimed invention, representative of applicant discussed the state of the art regarding irinotecan containing liposomes. Representative of applicant explained that liposomes, especially those comprising camptothecin or derivatives thereof as the active agent (of which irinotecan is a camptothecin derivative) have a problem with degradation in storage. While such a liposome can be prepared, such liposomal preparations will degrade when stored for multiple months in the refrigerator.

Representative of applicant explained that the problem with such liposomes in the prior art is that the phosphatidylcholine, which is a phospholipid with two alkyl chains, degrades to lysophosphatidylcholine, which is a phospholipid with one alkyl chain. This loss of

subsequently leaves the liposome, resulting in drug leakage from the liposome.

Representative of applicant explained that the instant invention set out to solve the problem of such drug leakage.

Representative also cited three references drawn to the state of the art; two references by Grit et al. and one reference by Sattern et al. Representative of applicant explains that these references teach that liposomal phosphatidylcholine is most stable to hydrolysis to lysophosphatidylcholine at a pH of about 6.25-6.5. Representative of applicant also cited Sattern as teaching that a camptothecin liposome has inadequate storage stability for a marketable pharmaceutical product, citing page 79, right column, bottom paragraph.

Other:

First, representative of applicant noted that prior art reference US 2007/0110798 A1 was incorrectly marked as 2007/0010798 A1 on the pre-interview communication. The examiner agrees that this was in error.

Secondly, the amendments submitted on 02/19/2017 have been entered. At the moment, the claimed invention of the claimes on 02/19/2017 does not appear to be rejected over prior art but the examiner must further consider these claims under 35 U.S.C. 112. The examiner may also wish to reconsider the decision not to reject the instant claims on the grounds of non-statutory double patenting.

As such, the amendment submitted on 02/19/2017 has been ENTERED and no PTO-413FA submitted. The next action will be provided by the examiner.

Attachment(s): Other, PTO-892 is attached along with non-patent literature references cited in said PTO-892.

/ISAAC SHOMER/ Primary Examiner, Art Unit 1612	

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

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

Applicant is reminded that a complete written statement as to the substance of the interview must be made of record in the application file. It is the applicant's responsibility to provide the written statement, unless the interview was initiated by the Examiner and the Examiner has indicated that a written summary will be provided. See MPEP 713.04

Please further see:

MPEP 713.04
Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews, paragraph (b)
37 CFR § 1.2 Business to be transacted in writing

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/337,274	10/28/2016	SARAH F. BLANCHETTE	239669-402970	4700

133156 7590 03/24/2017

Honigman Miller Schwartz and Cohn LLP
350 East Michigan Avenue
Suite 300
Kalamazoo, MI 49007

EXAMINER
PACKARD, BENJAMIN J

ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
03/24/2017	ELECTRONIC

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

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

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

patents@honigman.com
lbroecker@honigman.com
lzerby@honigman.com

Office Action Summary	Application No. 15/337,274	Applicant(s) BLANCHETTE ET AL.	
	Examiner BENJAMIN PACKARD	Art Unit 1612	AIA (First Inventor to File) Status Yes

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

Period for Reply

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

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

Status

1)☐ Responsive to communication(s) filed on _____.

☐ 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) *21-40* 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) *21-40* 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 _____ 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 *5pgs (10/28/16)*.

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

4) ☐ Other: _____.

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

Claim Rejections - 35 USC § 112

The following is a quotation of 35 U.S.C. 112(b):
(b) CONCLUSION.—The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), second paragraph:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 28-33 are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention.

The claims recite the use of MM-398, which according to the specification at ¶ 6, is Onivyde®, a trademarked product. Given the trademark and designator are directed to a name, and not a specific composition, it is unclear what the specific composition claimed is. Examiner suggest either liposomal irinotecan or the specific liposomal formulation/components used, e.g. liposomal (55:45 mol% DSPC/Chol).

Claim Rejections - 35 USC § 102

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.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a)(1) the claimed invention was patented, described in a printed publication, or in public use, on sale or otherwise available to the public before the effective filing date of the claimed invention.

Claim(s) 21-40 is/are rejected under 35 U.S.C. 102(a)(1) as being anticipated by Clinical Trials Archive (NCT02631733, updated Dec 12, 2015), pp1-6).

Clinical Trials Archive discloses a phase I trial of veliparib administered with liposomal irinotecan for treating patients with solid tumors (brief summary). Liposomal irinotecan is administered on days 1 and 15, with veliprarib administered on days 5-12 and 19-25 or 3-12 and 17-58, the course repeated every 28 days (pg 3).

Note, it is unclear from the reference whether one of the exceptions, 102(b)(1)(A) or 102(b)(1)(B) applies, therefore this art is applied pending evidence showing the study was granted by the inventor.

Claim Rejections - 35 USC § 103

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

> A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

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 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.

Claims 21-40 is/are rejected under 35 U.S.C. 103 as being unpatentable over Messerer et al (Ciln Can Rsch, Oct 2004, vol 10, no 19, pp 6638-6649) in view of Genther-WIlliams et al (Cancer Cell Intrl, 2015, 15:14, pp 1-11).

Messerer et al teaches liposomal irinotecan (55:45 mol% DSPC/Chol, ~100nm in diameter) has enhanced therapeutic activity compared to irinotecan for treatment of solid tumors, including colorectal cancers (pg 6646, Discussion). It is also taught that irinotecan is often co-administered with additional agents to provide optimal therapeutic effects as judged by assays that measure the interactions between selected drug combinations (pg 6647, right col). Irinotecan is taught to be suitable for treatment of various tumor types, including breast, lung, and colorectal tumors (pg 6638, Introduction).

Genther-WIlliams et al teaches that the PARP inhibitor, niraparib, potentials the effect of irinotecan on colorectal cancer cells (pg 10, left col, last paragraph). The

dosing regimen for in vivo xenograft studies included weekly dosages of irinotecan and niraparib on each day for 3, 5, or 7 days (pg 3, left col, last paragraph).

It would have been obvious to one of ordinary skill in the art to administer the liposomal irinotecan in the treatment of solid tumors, including breast and colorectal cancer, given the increased efficacy over free irinotecan.

Further, as suggested by Messerer and supported by Genther-Williams, it would have been obvious to co-administer PARP inhibitors, such as niraparib, to provide increased activity of the irinotecan.

With regards to the specific regimen, Genther-Williams suggests administering the irinotecan weekly with the PARP inhibitor administered during the interval. Optimizing the specific for optimum therapeutic results appears to be obvious in light of Genther-Williams, given the teaching that the niraparib may be varying over set intervals of days in relation to the irinotecan co-administered.

Claims 21-40 is/are rejected under 35 U.S.C. 103 as being unpatentable over U.S. Patent No. 8,147,867 in view of Genther-WIlliams et al (Cancer Cell Intrl, 2015, 15:14, pp 1-11).

‘867 discloses liposomal irinotecan as an anti-tumor agents (claim 1) but not co-administration of PARP inhibitors.

Genther-WIlliams et al is discussed above for teaching co-administration of PARP inhibitors and varying the dosage regimen in order to optimize the therapeutic effect.

It would have been obvious to one of ordinary skill in the art to use the liposomal irinotecan in the method of Genther-Williams et al, given in benefit of increased bioavailability of the liposomal irinotecan.

Obvious-Type 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 21-40 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-35 of U.S. Patent No. 8,147,867 in view of Genther-WIlliams et al (Cancer Cell Intrl, 2015, 15:14, pp 1-11).

‘867 discloses liposomal irinotecan as an anti-tumor agents (claim 1) but not co-administration of PARP inhibitors.

Genther-WIlliams et al is discussed above for teaching co-administration of PARP inhibitors and varying the dosage regimen in order to optimize the therapeutic effect.

It would have been obvious to one of ordinary skill in the art to use the liposomal irinotecan in the method of Genther-Williams et al, given in benefit of increased bioavailability of the liposomal irinotecan.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BENJAMIN PACKARD whose telephone number is (571)270-3440. The examiner can normally be reached on M-R 8-6 EST.

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, Frederick Krass can be reached on 571-272-0580. 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.

/BENJAMIN PACKARD/
Primary Examiner, Art Unit 1612

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/341,377	11/02/2016	Eliel Bayever	239669-375517	1133

133156 7590 01/30/2017

Honigman Miller Schwartz and Cohn LLP
350 East Michigan Avenue
Suite 300
Kalamazoo, MI 49007

EXAMINER
STRONG, TORI

ART UNIT	PAPER NUMBER
1629	

NOTIFICATION DATE	DELIVERY MODE
01/30/2017	ELECTRONIC

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

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

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

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lbroecker@honigman.com
lzerby@honigman.com

Office Action Summary	Application No. 15/341,377	Applicant(s) BAYEVER ET AL.	
	Examiner TORI M. STRONG	Art Unit 1629	AIA (First Inventor to File) Status No

-- 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 *02 November 2016*.

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

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

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; 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) *1-10* is/are pending in the application.

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

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-10* 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 *02 November 2016* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

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

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

Priority under 35 U.S.C. § 119

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

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

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

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

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

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

Attachment(s)

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

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

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

4) ☐ Other: _____.

DETAILED ACTION

Notice of Pre-AIA or AIA Status

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

Status of Claims

Claims 1-10 are pending in the instant application and are the subject of the Office Action below.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on November 02, 2016 was filed on the mailing date of the application on. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner. Enclosed with this Office Action are return copies of Form PTO/SB/08B with the Examiner's initials and signature indicating those references that have been considered.

Claim Rejections - 35 USC § 103

The following is a quotation of pre-AIA 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, 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.

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 pre-AIA 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.

This application currently names joint inventors. In considering patentability of the claims under pre-AIA 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 pre-AIA 35 U.S.C. 103(c) and potential pre-AIA 35 U.S.C. 102(e), (f) or (g) prior art under pre-AIA 35 U.S.C. 103(a).

Claim 1-4 and 6-10 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Chen *et al.* (*Journal of Clinical Oncology*, 2008, Vol. 26, No. 15S, p. 2565; cited in IDS) and Kozuch *et al.* (*The Oncologist*, 2001, 6, pp. 488-495; cited in IDS).

Applicant's invention, according to **claims 1 and 6**, is directed to a method of treating solid tumor comprising administering a single dose of 60, 70, 80, 120 or 180 mg/m^2 MM-398 liposomal irinotecan once every two weeks intravenously; where claim 6 requires intravenous infusion over 90 minutes.

Chen teaches treatment of advanced refractory solid tumors where pancreatic cancer is an exemplified embodiment and the patients are refractory to standard chemotherapy. Chen teaches the liposomal formulation of irinotecan referred to as PEP02, which is the same as MM-398, as evidenced by Tsai *et al.* (*Journal of Gastrointestinal Oncology,* 2011, Vol. 2, pp. 185-194; cited in IDS) (see Tsai *et al.*, p.189, col.2, para.2). Chen teaches administering doses of PEP02 at 60, 120 and 180 mg/m^2, thus meeting the instantly claimed limitation of dose range, through intravenous infusion over 90 minutes. Chen teaches the improvements of PEP02 (or MM-398) over the free form, where the terminal half-life is about 29.5 hours. While Chen explicitly teaches the intravenous infusion of PEP02, Chen does not teach a cycle of administration of every two weeks.

Kozuch teaches a method of treating metastatic pancreatic cancer refractory to gemcitabine therapy through administration of a combination called G-FLIP which comprises irinotecan (80 mg/m^2) (abs). Kozuch teaches adminsitration of irinotecan, referred to as CPT-11, over 90 minutes (p.490, Fig.1). Kozuch provides a composition that comprises irinotecan at 80 mg/m^2 and teaches administration once every two weeks (abs).

One of ordinary skill would arrive at the instant claims of administering MM-398 at a given claimed dose for treating solid tumor in a two week cycle having a reasonable expectation of success based on the combined teaching of Chen and Kozuch. Chen provides explicit teaching of the dose, form and method of administration of the MM-398, demonstrating improved benefit over the free form. Kozuch provides guidance to administration of the free form of irinotecan in a two week cycle. A skilled artisan would gleam from Kozuch that administration of irinotecan in a two week cycle is beneficial and from Chen that the liposomal form of irinotecan, MM-398, is an improved form of irinotecan. Therefore at the time of invention, it was *prima facie* obvious to arrive at the instant claims based on the combined teaching of Chen and Kozuch.

Applicant's invention, according to **claims 2 and 3**, limits claim 1 and requires a portion of the irinotecan is converted to the metabolite SN-38 and the total AUC of SN-38 in the plasma increases less than proportionally with dose of total irinotecan; administered in the MM-398 form. Where claim 3 requires that AUC of irinotecan in the plasma increases less than proportionally with the dose of total irinotecan.

As expressed *supra*, Chen teaches the use of PEP02 for treating advanced pancreatic cancer refractory to therapy. Chen also teaches the active metabolite SN-38; disclosing a C_{max} of about 9.2 + 3.5 ng/mL, a $t_{1/2}$ of about 75.4 $\pm$ 43.8 hours, an AUC at about 710 $\pm$ 395 ng.h/mL and further disclosing "...that the release of irinotecan from the liposomes occurred slowly over time." The values disclosed by Chen for the SN-38 profile meet the instantly claimed limitation. Chen's teaching of the irinotecan slowly

releasing also meets the limitation of its active metabolite increasing slowly compared to the dose of the liposome form. The instant limitations read upon the art of Chen and therefore the invention as a whole remains *prima facie* obvious over Chen and Kozuch.

Applicant's invention, according to **claims 4 and 7-10**, limits claim 1 and requires all the limitations of claims 1-3 and 6 with the addition of the patient not being homozygous for the UGT1A1*28 allele.

The overall teaching of Chen and Kozuch is directed to patients with solid tumors where the patients were not described to be homozygous for the UGT1A1*28 allele. Therefore the teaching as expressed *supra*, applies to the same patient population instantly claimed, unless evidence to the contrary; and thus the rejection applied *supra*, applies to the instant claims. Therefore, for reasons stated supra, the instant claims remain prima facie obvious based on the combined teaching of Chen and Kozuch.

Claims 1 and 5 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Chen *et al.* (*Journal of Clinical Oncology*, 2008, Vol. 26, No. 15S, p. 2565; cited in IDS) and Kozuch *et al.* (*The Oncologist*, 2001, 6, pp. 488-495; cited in IDS), in view of Hoskins *et al.* (*J. Natl. Cancer Inst.*, 2007, Vol. 99, Iss. 17, pp. 1290-1295; cited in IDS).

Applicant's invention, according to **claim 5**, limits claim 1 and requires administration at 60 mg/m^2 of MM-398 to patients homozygous for the UGT1A1*28 allele.

A case of *prima facie* obviousness is established for administering 60 mg/m^2 of MM-398 for solid tumors in a two week cycle based on the teachings Chen and Kozuch. Neither disclosure teaches the patient to be homozygous for the UGT1A1*28 allele.

Hoskins teaches the effect of irinotecan on patients with UGT1A1*28 genotype. Hoskins teaches that there is an association with irinotecan-induced toxicities with patients who were homozygous for UGT1A1*28 allele (p.1290, para.2). Hoskins teaches that hematologic toxicity, neutropenia, or diarrhea was associated with irinotecan administration but not clarified as to the relationship. Hoskins further teaches that when the toxicities were further assessed, the relationship reveals that dosing of irinotecan caused different effects (p.1291, para.2). Hoskins teaches three categories of dosing; high doses (200-350 mg/m^2), intermediate dose (180 mg/m^2) and low doses (80-125 mg/m^2) where the hematologic toxicity, neutropenia, is associated with high doses of irinotecan in patients that are homozygous for UGT1A1*28 allele; and teaches that low doses the risk is the same with other genotypes (p.1293, para.3). Therefore one of ordinary skill in the art would readily utilize a low dose of irinotecan for patients that are homozygous for UGT1A1*28 allele knowing that any dosing lower than 125 mg/m^2 would generally not cause neutropenia.

One of ordinary skill would arrive at the instant limitation of administering a low dose of 60 mg/m^2 of MM-398 to a patient that is homozygous for UGT1A1*28 allele

having a reasonable expectation of success based on Chen, Kozuch and Hoskins. Hoskins provides guidance for skilled artisans to gleam that low doses, below 125 mg/m2, of irinotecan minimizes the toxic effects particularly in patients that are homozygous for UGT1A1*28 allele. Therefore the invention as a whole remains *prima facie* obvious with the incorporation of the instant limitation based on the combined teaching of Chen, Kozuch and Hoskins.

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 1-10 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1, 3-5 and 18 of copending Application No. 15/059,640; claims 1-24 of copending Application No. 15/241,128; and claims 1-20 of copending Application No. 15/341,619. Although the claims at issue are not identical, they are not patentably distinct from each other because each disclosure sets out to

treat solid tumors through administration of liposomal irinotecan, MM-398 recognizing the metabolite SN-38 as an active component. The claimed inventions are variants of each other and thus the nonstatutory double-patenting rejection is applied.

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

Claims 1-10 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-27 of U.S. Patent No. 9,339,497 B2; claims 1-29 of U.S. Patent No. 9,364,473 B2; claims 1-35 of U.S. Patent No. 9,452,162 B2; and claims 1-30 of U.S. Patent No. 9,492,442 B2. Although the claims at issue are not identical, they are not patentably distinct from each other because each disclosure sets out to treat solid tumors through administration of liposomal irinotecan, MM-398, over a two week period. The claimed inventions are more specific embodiments which anticipate the instant claims and thus the nonstatutory double-patenting rejection is applied.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TORI M. STRONG whose telephone number is (571)272-6333. The examiner can normally be reached on Monday-Friday 8am-5pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Lundgren can be reached on 571-272-5541. 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.

/TORI M STRONG/
Examiner, Art Unit 1629

/Kortney L. Klinkel/
Primary Examiner, Art Unit 1611

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/341,377	11/02/2016	Eliel Bayever	239669-375517	1133

133156 7590 04/18/2017

Honigman Miller Schwartz and Cohn LLP
Merrimack
350 East Michigan Avenue
Suite 300
Kalamazoo, MI 49007

EXAMINER
STRONG, TORI

ART UNIT	PAPER NUMBER
1629	

NOTIFICATION DATE	DELIVERY MODE
04/18/2017	ELECTRONIC

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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):

patents@honigman.com
lbroecker@honigman.com
lzerby@honigman.com

Office Action Summary	Application No. 15/341,377	Applicant(s) BAYEVER ET AL.	
	Examiner TORI M. STRONG	Art Unit 1629	AIA (First Inventor to File) Status No

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

Period for Reply

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Status

1)☒ Responsive to communication(s) filed on *07 February 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) *2,3,6 and 10-15* 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) *2,3,6 and 10-15* 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 _____ 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)).

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Attachment(s)

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

4) ☐ Other: _____.

DETAILED ACTION

Notice of Pre-AIA or AIA Status

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

Status of Claims

Claims 2, 3, 6, 10-15 are pending in the instant application; claims 2, 3 and 6 are amended; claims 1, 4, 5 and 7-9 are cancelled; claims 11-15 are newly presented; claims 2, 3, 6, 10-15 are the subject of the Office Action below.

Examination Considerations

Applicant's Amendments filed February 7, 2017 have been received and entered into the present application. Claims 2, 3, 6, 10-15 are pending and are herein examined on the merits.

Applicant's Arguments, filed February 7, 2017 have been fully considered. Rejections not reiterated from previous Office Actions are hereby withdrawn. The following rejections are either reiterated or newly applied. They constitute the complete set of rejections presently being applied to the instant application.

Applicant's Terminal Disclaimer, filed February 7, 2017 is acknowledged and approved.

Claim Rejections - 35 USC § 103 – Maintained and Modified (Necessitated by Amendment)

The following is a quotation of pre-AIA 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, 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.

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 pre-AIA 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.

This application currently names joint inventors. In considering patentability of the claims under pre-AIA 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 pre-AIA 35 U.S.C. 103(c) and potential pre-AIA 35 U.S.C. 102(e), (f) or (g) prior art under pre-AIA 35 U.S.C. 103(a).

Claims 2, 3, 6 and 10 rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Chen *et al.* (*Journal of Clinical Oncology*, 2008, Vol. 26, No. 15S, p. 2565; cited in IDS) and Kozuch *et al.* (*The Oncologist*, 2001, 6, pp. 488-495; cited in IDS) is ***maintained*** and ***modified***.

Response to Applicant's Arguments:

Applicant traverses rejection and alleges the combination does not arrive at the claimed method because Chen does not teach 80 mg/m^2 MM-398 liposomal irinotecan every two weeks and that Kozuch does not disclose liposomal form of irinotecan.

Applicant's arguments are found unpersuasive for reasons of record. Applicant is reminded that the rejection (mailed 01/30/2017) points out that Chen teaches administration of PEP02, which is the same as MM-398, at dosing that demonstrates a range from 60 to 180 mg/m^2. The instantly claimed dose is well within the range of dosing that Chen explicitly utilizes for treating the same patient population, using the same formulation along with the same method of infusion administration over 90 minutes. The only real distinction between the prior art and the instant claim is the cycle of two week administration. Kozuch teaches treating a solid tumor with irinotecan at the instantly claimed dose of 80 mg/m^2 in a two week cycle. It is important to note that Chen and Kozuch demonstrate treatment of solid tumors with liposomal irinotecan and non-liposomal irinotecan in the same overall dosing range. There is a clear nexus for treating solid tumors with irinotecan within the claimed dosing range in two or three week cycles based on the combined teaching; where Chen explicitly teaches

administration of liposomal form of irinotecan. Applicant provides no evidence of unexpected results, where there is a reasonable expectation of success in treating solid tumors with liposomal irinotecan in the overall dosing range over a few weeks cycle; particularly when both disclosures demonstrate that treatment can be conferred with irinotecan in liposomal form or non-liposomal form at the same dosing range. Applicant's argument is found unpersuasive and the instant claims remain *prima facie* obvious over the prior art of record.

Modified Rejection:

Applicant's invention, according to **claims 10 and 6**, is directed to a method of treating solid tumor comprising administering a single dose of 80 mg/m^2 MM-398 liposomal irinotecan once every two weeks intravenously with the patient not being homozygous for the UGT1A1*28 allele; where claim 6 requires intravenous infusion over 90 minutes.

Chen teaches treatment of advanced refractory solid tumors where pancreatic cancer is an exemplified embodiment and the patients are refractory to standard chemotherapy. Chen teaches the liposomal formulation of irinotecan referred to as PEP02, which is the same as MM-398, as evidenced by Tsai et al. (Journal of Gastrointestinal Oncology, 2011, Vol. 2, pp. 185-194; cited in IDS) (see Tsai et al., p.189, col.2, para.2). Chen teaches administering doses of PEP02 at 60, 120 and 180 mg/m^2, thus meeting the instantly claimed limitation of dose range, through intravenous infusion over 90 minutes. Chen teaches the improvements of PEP02 (or MM-398) over

the free form, where the terminal half-life is about 29.5 hours. While Chen explicitly teaches the intravenous infusion of PEP02, Chen does not teach a cycle of administration of every two weeks.

Kozuch teaches a method of treating metastatic pancreatic cancer refractory to gemcitabine therapy through administration of a combination called G-FLIP which comprises irinotecan (80 mg/m2) (abs). Kozuch teaches adminsitration of irinotecan, referred to as CPT-11, over 90 minutes (p.490, Fig.1). Kozuch provides a composition that comprises irinotecan at 80 mg/m2 and teaches administration once every two weeks (abs).

The overall teaching of Chen and Kozuch is directed to patients with solid tumors where the patients were not described to be homozygous for the UGT1A1*28 allele. Therefore the teaching as expressed *supra*, applies to the same patient population instantly claimed, unless evidence to the contrary.

One of ordinary skill would arrive at the instant claims of administering MM-398 at a given claimed dose for treating solid tumor in a two week cycle having a reasonable expectation of success based on the combined teaching of Chen and Kozuch. Chen provides explicit teaching of the dose, form and method of administration of the MM-398, demonstrating improved benefit over the free form. Kozuch provides guidance to administration of the free form of irinotecan in a two week cycle. A skilled artisan would gleam from Kozuch that administration of irinotecan in a two week cycle is beneficial and from Chen that the liposomal form of irinotecan, MM-398, is an improved form of

irinotecan. Therefore at the time of invention, it was *prima facie* obvious to arrive at the instant claims based on the combined teaching of Chen and Kozuch.

Applicant's invention, according to **claims 2 and 3**, limits claim 10 and requires a portion of the irinotecan is converted to the metabolite SN-38 and the total AUC of SN-38 in the plasma increases less than proportionally with dose of total irinotecan; administered in the MM-398 form. Where claim 3 requires that AUC of irinotecan in the plasma increases less than proportionally with the dose of total irinotecan.

As expressed *supra*, Chen teaches the use of PEP02 for treating advanced pancreatic cancer refractory to therapy. Chen also teaches the active metabolite SN-38; disclosing a C_{max} of about 9.2 $\pm$ 3.5 ng/mL, a $t_{1/2}$ of about 75.4 $\pm$ 43.8 hours, an AUC at about 710 $\pm$ 395 ng.h/mL and further disclosing "...that the release of irinotecan from the liposomes occurred slowly over time." The values disclosed by Chen for the SN-38 profile meet the instantly claimed limitation. Chen's teaching of the irinotecan slowly releasing also meets the limitation of its active metabolite increasing slowly compared to the dose of the liposome form. The instant limitations read upon the art of Chen and therefore the invention as a whole remains *prima facie* obvious over Chen and Kozuch.

New Grounds of Rejection

Claims 11-13 and 15 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Chen *et al.* (*Journal of Clinical Oncology*, 2008, Vol. 26, No. 15S, p. 2565; cited in IDS) and Kozuch *et al.* (*The Oncologist*, 2001, 6, pp. 488-495; cited in

IDS), in view of Hoskins *et al.* (*J. Natl. Cancer Inst.*, 2007, Vol. 99, Iss. 17, pp. 1290-1295; cited in IDS).

Applicant's invention, according to **claims 11-13 and 15**, is directed to a method of treating solid tumor in a patient homozygous for the UGT1A1*28 allele comprising administering a single dose of 60 mg/m^2 MM-398 liposomal irinotecan once every two weeks intravenously where a portion of the irinotecan is converted to the metabolite SN-38 and wherein a) the total AUC of SN-38 in the plasma increases less than proportionally with dose of total irinotecan administered in the MM-398 form and b) the total AUC of irinotecan in the plasma increases less than proportionally with the dose of total irinotecan.

A case of *prima facie* obviousness is established for intravenously administering 60 mg/m^2 of MM-398 for solid tumors in a two week cycle where the instantly claimed functionality of conversion to SN-38 metabolite occurs at certain increase relative to the dose based on the teachings Chen and Kozuch as set forth above. Neither disclosure teaches the patient to be homozygous for the UGT1A1*28 allele.

Hoskins teaches the effect of irinotecan on patients with UGT1A1*28 genotype. Hoskins teaches that there is an association with irinotecan-induced toxicities with patients who were homozygous for UGT1A1*28 allele (p.1290, para.2). Hoskins teaches that hematologic toxicity, neutropenia, or diarrhea was associated with irinotecan administration but not clarified as to the relationship. Hoskins further teaches that when the toxicities were further assessed, the relationship reveals that dosing of

irinotecan caused different effects (p.1291, para.2). Hoskins teaches three categories of dosing; high doses (200-350 mg/m^2), intermediate dose (180 mg/m^2) and low doses (80-125 mg/m^2) where the hematologic toxicity, neutropenia, is associated with high doses of irinotecan in patients that are homozygous for UGT1A1*28 allele; and teaches that at low doses the risk is the same with other genotypes (p.1293, para.3). Therefore one of ordinary skill in the art would readily utilize a low dose of irinotecan for patients that are homozygous for UGT1A1*28 allele knowing that any dosing lower than 125 mg/m^2 would generally not cause neutropenia.

One of ordinary skill would arrive at the instant limitation of administering a low dose of 60 mg/m^2 of MM-398 to a patient that is homozygous for UGT1A1*28 allele having a reasonable expectation of success based on Chen, Kozuch and Hoskins. Hoskins provides guidance for skilled artisans to gleam that low doses, below 125 mg/m^2, of irinotecan minimizes the toxic effects particularly in patients that are homozygous for UGT1A1*28 allele. Therefore the invention as a whole remains *prima facie* obvious with the incorporation of the instant limitation based on the combined teaching of Chen, Kozuch and Hoskins.

Claim 14 is rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Chen *et al.* (*Journal of Clinical Oncology*, 2008, Vol. 26, No. 15S, p. 2565; cited in IDS) and Kozuch *et al.* (*The Oncologist*, 2001, 6, pp. 488-495; cited in IDS).

Applicant's invention, according to **claim 14**, is directed to a method of treating solid tumor in a patient not being homozygous for the UGT1A1*28 allele comprising administering a single dose of 80 mg/m^2 MM-398 liposomal irinotecan once every two weeks intravenously where a portion of the irinotecan is converted to the metabolite SN-38 and wherein a) the total AUC of SN-38 in the plasma increases less than proportionally with dose of total irinotecan administered in the MM-398 form and b) the total AUC of irinotecan in the plasma increases less than proportionally with the dose of total irinotecan.

For the reasons expressed for claims 10, 2 and 3, *supra*, the rejection is applied to the instant claim 14. Chen teaches the use of PEP02, or MM-398, for treating a solid tumor in a dosing range as instantly claimed through intravenous administration where the irinotecan is converted to the metabolite SN-38 providing the AUC functionality as instantly claimed. Kozuch teaches treating solid tumors with irinotecan at 80 mg/m^2 over a two week cycle. For the reasons stated *supra* for claims 10, 2 and 3, it was *prima facie* obvious to arrive at the instant claim based on the combined teaching of Chen and Kozuch.

Double Patenting - Withdrawn

Claims 1-10 provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1, 3-5 and 18 of copending Application No. 15/059,640; claims 1-24 of copending Application No. 15/241,128; and claims 1-20 of copending Application No. 15/341,619 is ***withdrawn***.

Claims 1-10 rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-27 of U.S. Patent No. 9,339,497 B2; claims 1-29 of U.S. Patent No. 9,364,473 B2; claims 1-35 of U.S. Patent No. 9,452,162 B2; and claims 1-30 of U.S. Patent No. 9,492,442 B2 is ***withdrawn***.

Applicant has filed a Terminal Disclaimer thus obviating the rejection. Therefore the rejection is withdrawn.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TORI M. STRONG whose telephone number is

(571)272-6333. The examiner can normally be reached on Monday-Friday 8am-5pm EST.

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, Jeffrey Lundgren can be reached on 571-272-5541. 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.

/TORI M STRONG/
Examiner, Art Unit 1629

/Kortney L. Klinkel/
Primary Examiner, Art Unit 1611

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/341,619	11/02/2016	Eliel Bayever	239669-404443	1049

133156 7590 04/03/2017

Honigman Miller Schwartz and Cohn LLP
350 East Michigan Avenue
Suite 300
Kalamazoo, MI 49007

EXAMINER
STRONG, TORI

ART UNIT	PAPER NUMBER
1629	

NOTIFICATION DATE	DELIVERY MODE
04/03/2017	ELECTRONIC

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

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

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

patents@honigman.com
lbroecker@honigman.com
lzerby@honigman.com

First Action Interview Pilot Program Pre-Interview Communication	Application No. 15/341,619	Applicant(s) BAYEVER ET AL.	
	Examiner TORI M. STRONG	Art Unit 1629	AIA (First Inventor to File) Status Yes

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

THE SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE **ONE MONTH OR THIRTY (30) DAYS,** WHICHEVER IS LONGER, FROM THE MAILING OR NOTIFICATION DATE OF THIS COMMUNICATION.

This time period for reply is extendable under 37 CFR 1.136(a) for only ONE additional MONTH.

This communication constitutes notice under 37 CFR 1.136(a)(1)(i).

Applicant must, within the time period for reply, file: (1) A letter requesting not to have a first action interview; (2) A reply under 37 CFR 1.111 waiving the first action interview and First Action Interview Office Action; or (3) An Applicant Initiated Interview Request Form (PTOL-413A) electronically via EFS-Web, accompanied by a proposed amendment or arguments, and schedule the interview within 2 months from the filing of the request. A failure to respond to this communication will be treated as a request not to have an interview. If applicant waives the First Action Interview Office Action, the instant Pre-Interview Communication is deemed the first Office Action on the Merits. The next subsequent Office action may be made final if appropriate. See MPEP 706.07(a).

Status

1)☒ Responsive to communication(s) filed on *02 November 2016*.

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

Disposition of Claims

2)☒ Claim(s) *1-20* is/are pending in the application.

2a) Of the above claim(s) _____ is/are withdrawn from consideration.

3)☐ Claim(s) _____ is/are allowed.

4)☒ Claim(s) ***1-20*** is/are rejected.

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

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

Application Papers

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

8)☒ The drawing(s) filed on *02 November 2016* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

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

a)☐ All b)☐ Some * c)☐ None of:

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.

Contact Information

Examiner's Telephone Number: (571)272-6333

Examiner's Typical Work Schedule: Monday-Friday 8am-5pm EST

Supervisor's Name: Jeffrey Lundgren

Supervisor's Telephone Number: (571)272-5541

Attachment(s)

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

2) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.

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

4) ☐ Other: _____.

First Action Interview Pilot Program Pre-Interview Communication	**Application No.** 15/341,619	**Applicant(s)** BAYEVER ET AL.	
	Examiner TORI M. STRONG	**Art Unit** 1629	**AIA (First Inventor to File) Status** Yes

Notification of Rejection(s) and/or Objection(s)

#	Claim(s)	Reference(s) (if applicable)	Rejection Statutory Basis	Brief Explanation of Rejection
1	1-20	33/50 (IDS 11/2/2016)	103(a)	33 teaches the method for treating solid tumors comprising administration of a single dose of liposomal irinotecan in the claimed dosing range where 50 teaches administering irinotecan (non-liposomal) at 80 mg/m2 for solid
2	1-20	A-F	Non-statutory Double Patenting	Each disclosure sets out to claim treatment of solid tumors comprising administration of liposomal irinotecan over a two week period
3	1-20		112(1)	The instantly claimed method of treating solid tumors with liposomal irinotecan requires claimed functions such as 25.8 half life, AUC increasing linearly, and converted metabolite SN-28 Cmax increasing proportionally.

Expanded Discussion/Commentary

1		tumors once every two weeks. 33 provides teaching of many of the claimed resultant functions where those that are unappreciated would be rendered obvious due the reasonable expectation of success in the active step of administration of the liposomal irinotecan in the claimed dose once in a two week cycle based on the combined 33/50 references.
3		Applicants have not provided guidance to the function being a result of the liposome surrounding the irinotecan or any liposome that can be used. Applicants don't provide descriptive support for every conceivable liposome that can encapsulate irinotecan to effectively cause the functions claimed therefore Applicants are not in possession of the claims. Thus the claims lack written descriptive support.

DATE: 23 March, 2017	/Kortney L. Klinkel/ Primary Examiner, AU 1611	/Tori M Strong/ Examiner, AU 1629

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/363,761	11/29/2016	Keelung Hong	239669-405184/1001130US18	1062

133156 7590 01/18/2017

Honigman Miller Schwartz and Cohn LLP
350 East Michigan Avenue
Suite 300
Kalamazoo, MI 49007

EXAMINER	
RONEY, CELESTE A	

ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
01/18/2017	ELECTRONIC

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

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

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

patents@honigman.com
lbroecker@honigman.com
lzerby@honigman.com

Office Action Summary	Application No. 15/363,761	Applicant(s) HONG ET AL.	
	Examiner CELESTE A. RONEY	Art Unit 1612	AIA (First Inventor to File) Status No

-- 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 *12/13/16*.

☐ 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) *1-10* is/are pending in the application.

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

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-10* 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 _____ 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 *11/29/16*.

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

4) ☐ Other: _____.

DETAILED ACTION

Notice of Pre-AIA or AIA Status

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

Claim Rejections - 35 USC § 103

The following is a quotation of pre-AIA 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, 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.

Claim 1 is rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Rahman et al (WO 2003/030864), in view of Matulic-Adamic et al (US 2002/0028919).

Rahman disclosed liposomal formulations of entrapped irinotecan, at the abstract and title. The liposomes comprised phospholipids, e.g., phosphatidylcholine, at claims 11 and 17. The compositions were useful in the treatment of cancer, at the abstract.

The compositions comprised 1-50 wt. % irinotecan and 1-95 wt. % phosphatidylcholine, at page 5 and lines 4-11. At 50 wt. % irinotecan (e.g., 0.5 ÷ 587 g/mol = 0.00085 mol) and 95 wt. % phosphatidylcholine (e.g., 0.95 ÷ 758 g/mol = 0.00125 mol), Rahman's molar ratio of irinotecan to phospholipid is 0.7:1 (e.g. 0.00085 ÷ 0.00125), which falls within the instantly recited range of 0.15:1 to 1.5:1.

Rahman did not disclose triphosphate, as recited in claim 1.

Matulic-Adamic disclosed nucleotide tri-phosphates (claims 1 and 3), as liposomal encapsulated [0087] anticancer agents, at [0032].

Matulic-Adamic did not disclose irinotecan.

Since Rahman disclosed the treatment of cancer with anticancer agents generally (abstract), it would have been prima facie obvious to one of ordinary skill in the art to have incorporated nucleotide tri-phosphates within Rahman, as taught by Matulic-Adamic. The MPEP, at section 2144.07, states that generally, it is *prima facie* obvious to select a known material for incorporation into a composition, based on its recognized suitability for its intended use. In the instant case, it is *prima facie* obvious to select a nucleotide tri-phosphate compound for incorporation into a composition, based on its recognized suitability for its intended use as an anticancer agent, as taught by Matulic-Adamic.

The instant claim 1 recites a 0.15:1 to 1.5:1 molar ratio of irinotecan to phospholipid. Rahman disclosed a 0.7:1 irinotecan to phospholipid molar ratio, as discussed above. In the case where the claimed ranges "overlap or lie inside ranges disclosed by the prior art", a prima facie case of obviousness exists. MPEP 2144.05 A.

Claims 2-3 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Rahman et al (WO 2003/030864), in view of Matulic-Adamic et al (US 2002/0028919) and further in view of Mentrup Edgar et al (USP 5,498,420).

The 35 U.S.C. 103(a) rejection over Rahman, in view of Matulic-Adamic has been discussed above. Additionally, Rahman disclosed, at claims 11 and 17, that the liposome forming material was phosphatidyl choline and cholesterol.

Although Rahman disclosed phosphatidyl choline as a lipid forming material, Rahman did not specifically disclose lecithin, as recited in claims 2-3.

However, Mentrup Edgar disclosed liposome vesicles comprised of phosphatidyl choline, wherein the phosphatidyl choline was in the form of a natural lecithin, at claims 1 and 5.

Mentrup Edgar did not disclose irinotecan.

Since Rahman disclosed liposomes comprised of phosphatidyl choline, it would have been prima facie obvious to one of ordinary skill in the art to have included lecithin within Rahman's composition, as taught by Mentrup Edgar. It is *prima facie* obvious to select lecithin for incorporation into a liposome, based on its recognized suitability for its intended use as a vesicle forming lipid, as taught by Mentrup Edgar at claims 1 and 5.

Claim 3 is rendered prima facie obvious because Rahman disclosed 1-95 wt. % of the liposome forming material (e.g., phosphatidyl choline and cholesterol), as discussed above.

At 95 wt. % phosphatidylcholine (e.g., lecithin) (e.g., 0.95 ÷ 758 g/mol = 0.00125 mol) and 30 wt. % cholesterol (e.g., 0.30 ÷ 387 g/mol = 0.0008 mol), Rahman's molar

ratio of phosphatidyl choline (e.g., lecithin) to cholesterol is the instantly recited 3:2 (e.g. 0.00125 ÷ 0.0008).

Claims 4-9 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Rahman et al (WO 2003/030864), in view of Matulic-Adamic et al (US 2002/0028919) and further in view of Ellens et al (US 2004/0013720).

The 35 U.S.C. 103(a) rejection over Rahman, in view of Matulic-Adamic has been discussed above.

Additionally, Rahman disclosed phospholipids as liposome-forming lipids, in general, at page 8 and lines 7-8.

However, Rahman did not specifically disclose DSPC, as recited in claims 4-5 and 8-9. Also, Rahman did not disclose an amphipathic polymer comprising a polyethylene glycol-lipid, as recited in claims 5-9.

Ellens disclosed liposomes as vesicular drug delivery vesicles, at the abstract. The liposomes comprised phospholipids, as vesicle forming lipids commonly known in the art; DSPC was specifically disclosed as said phospholipid, at [0023-0025].

Polyethylene glycols (PEG) (e.g., hydrophilic polymer) were disclosed to increase blood circulation times, and to provide improved delivery of the liposomes, at [0014 and 0038]. The polyethylene glycols were disclosed as methoxy-capped (e.g., mPEG), and as having a molecular weight of about 300-7,000, at [0040]. Finally, the PEG was disclosed as PEG-DSPE (e.g., mPEG-DSPE), at 0-20 mole percent, at [0082].

Ellens did not disclose a triphosphate.

Since Rahman disclosed liposomes generally comprised of phospholipids as vesicle forming lipids, it would have been prima facie obvious to one of ordinary skill in the art to have included DSPC within Rahman, as taught by Ellens. An ordinarily skilled artisan would have been motivated because DSPC is commonly known in the art as a liposome vesicle forming lipid, as taught by Ellens at [0023-0025]. Further, It is *prima facie* obvious to select DSPC for incorporation into a liposome, based on its recognized suitability for its intended use as a vesicle forming lipid, as taught by Ellens.

Since Rahman disclosed liposomes, it would have been prima facie obvious to one of ordinary skill in the art to have incorporated an amphipathic polymer comprising a polyethylene glycol (e.g., mPEG-DSPE) within Rahman, as taught by Ellens. An ordinarily skilled artisan would have been motivated because said polymers provide improved delivery of the liposomes, as taught by Ellens at [0014 and 0038].

Claim 4 recites DSPC and cholesterol in a 3:2 mole ratio. Rahman disclosed 1-95 wt. % of the liposome forming material (e.g., phospholipids and cholesterol), as discussed above. Ellens disclosed DSPC as a commonly known phospholipid, as discussed above.

At 95 wt. % DSPC (e.g., 0.95 ÷ 790 g/mol = 0.0012 mol) and 30 wt. % cholesterol (e.g., 0.30 ÷ 387 g/mol = 0.0008 mol), Rahman's molar ratio of phospholipid (e.g., DSPC) to cholesterol is the instantly recited 3:2 (e.g. 0.0012 ÷ 0.0008).

Claims 5-7 are rendered prima facie obvious because Ellens disclosed mPEG-DSPE having a molecular weight of 300-7,000, as discussed above.

Claim 7 recites a PEG-DSPE molecular weight of from about 250 to about 20,000. Ellens disclosed mPEG-DSPE with a molecular weight of 300-7,000. A prima facie case of obviousness exists because of overlap, as discussed above.

Claims 8-9 are rendered prima facie obvious because Rahman disclosed a 3:2 molar ratio of phospholipid to cholesterol, as discussed above. Ellens disclosed DSPC, as discussed above. Further, Ellens disclosed PEG-DSPE (e.g., mPEG-DSPE), at 0-20 mole percent, as discussed above.

Claims 8-9 recite mPEG-DSPE at 0.015 mole. Further, claim 9 recites a molecular weight of PEG of 2,000. Ellens disclosed mPEG-DSPE at 0-20 mole. Additionally, Ellens disclosed PEG having a molecular weight of 300-7,000 as discussed above. A prima facie case of obviousness exists because of overlap, as discussed above.

Claim 10 is rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Rahman et al (WO 2003/030864), in view of Matulic-Adamic et al (US 2002/0028919) and further in view of Abai et al (WO 1990/014074).

The 35 U.S.C. 103(a) rejection over Rahman, in view of Matulic-Adamic has been discussed above.

Additionally, Rahman disclosed that the liposomes can be formed of negatively charged lipids, at page 4 and line 34. However, Rahman did not disclose the molar amount of phospholipids, as recited in claim 10.

Abai disclosed liposomal formulations comprised of at least 1 mole percent of negatively charged phospholipids, at claim 1.

Abai did not disclose irinotecan.

Since Rahman disclosed liposomes comprised of negative phospholipids, it would have been prima facie obvious to one of ordinary skill in the art to have included said phospholipids within Rahman at the amount of 1 mole, as taught by Abai. An ordinarily skilled artisan would have been motivated to have included the phospholipid in an amount sufficient to form the liposome, as taught by Abai at claim 1. An ordinarily skilled artisan would have been motivated to have included negatively charged phospholipids within Rahman at 1 mole, because at said amount, the ingredients are vesicle forming lipids, as taught by Abai.

Claim 10 recites 132.9 g of irinotecan and 1 mole of phospholipid. Rahman disclosed 1-50 wt. % irinotecan and 1-95 wt. % phosphatidylcholine, as discussed above. At 1-50 wt. % irinotecan is 5.87-294 g (e.g., 0.01-0.5 * 587 g/mole). Abai disclosed at least 1 mole percent of a negative phospholipid. A prima facie case of obviousness exists because of overlap, as discussed above.

Nonstatutory Double Patenting

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 1-10 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-20 of copending Application No. 14/964,299, in view of Matulic-Adamic et al (US 2002/0028919).

Although the claims at issue are not identical, they are not patentably distinct from each other. The copending claims recite all of the features instantly recited for the liposome except for a triphosphate. The instant claims require a triphosphate, and such an ingredient is not recited by the copending claims.

Matulic-Adamic disclosed nucleotide tri-phosphates as liposomal encapsulated anticancer agents.

It would have been prima facie obvious to one of ordinary skill in the art to have included trip-phosphates in the copending formulation, because triphosphates are anti-cancer agents, as discussed above, and as taught by Matulic-Adamic.

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

Claims 1-10 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-16 of copending Application No. 14/966,458, in view of Matulic-Adamic et al (US 2002/0028919).

Although the claims at issue are not identical, they are not patentably distinct from each other. The copending claims recite all of the features instantly recited for the liposome except for a triphosphate. The instant claims require a triphosphate, and such an ingredient is not recited by the copending claims.

Matulic-Adamic disclosed nucleotide tri-phosphates as liposomal encapsulated anticancer agents.

It would have been prima facie obvious to one of ordinary skill in the art to have included trip-phosphates in the copending formulation, because triphosphates are anti-cancer agents, as discussed above, and as taught by Matulic-Adamic.

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

Claims 1-10 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-24 of copending Application No. 15/364,021, in view of Matulic-Adamic et al (US 2002/0028919).

Although the claims at issue are not identical, they are not patentably distinct from each other. The copending claims recite all of the features instantly recited for the liposome except for a triphosphate. The instant claims require a triphosphate, and such an ingredient is not recited by the copending claims.

Matulic-Adamic disclosed nucleotide tri-phosphates as liposomal encapsulated anticancer agents.

It would have been prima facie obvious to one of ordinary skill in the art to have included trip-phosphates in the copending formulation, because triphosphates are anti-cancer agents, as discussed above, and as taught by Matulic-Adamic.

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

Claims 1-10 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-19 of copending Application No. 15/363,923, in view of Matulic-Adamic et al (US 2002/0028919).

Although the claims at issue are not identical, they are not patentably distinct from each other. The copending claims recite all of the features instantly recited for the liposome except for a triphosphate. The instant claims require a triphosphate, and such an ingredient is not recited by the copending claims.

Matulic-Adamic disclosed nucleotide tri-phosphates as liposomal encapsulated anticancer agents.

It would have been prima facie obvious to one of ordinary skill in the art to have included trip-phosphates in the copending formulation, because triphosphates are anti-cancer agents, as discussed above, and as taught by Matulic-Adamic.

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

Claims 1-10 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-10 of copending Application No. 15/363,978, in view of Matulic-Adamic et al (US 2002/0028919).

Although the claims at issue are not identical, they are not patentably distinct from each other. The copending claims recite all of the features instantly recited for the liposome except for a triphosphate. The instant claims require a triphosphate, and such an ingredient is not recited by the copending claims.

Matulic-Adamic disclosed nucleotide tri-phosphates as liposomal encapsulated anticancer agents.

It would have been prima facie obvious to one of ordinary skill in the art to have included trip-phosphates in the copending formulation, because triphosphates are anti-cancer agents, as discussed above, and as taught by Matulic-Adamic.

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

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CELESTE A. RONEY whose telephone number is (571)272-5192. The examiner can normally be reached on Monday-Thursday; 7A-5P.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Fred Krass can be reached on 571-272-0580. 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.

/CELESTE A. RONEY/
Examiner, Art Unit 1612

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/363,761	11/29/2016	Keelung Hong	263266-411568	1062

139696 7590 08/01/2017

Honigman Miller Schwartz and Cohn LLP/Ipsen
350 East Michigan Avenue, Suite 300
Kalamazoo, MI 49007

EXAMINER	
RONEY, CELESTE A	

ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
08/01/2017	ELECTRONIC

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

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

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

patents@honigman.com
lzerby@honigman.com
anelson@honigman.com

Office Action Summary	Application No. 15/363,761	Applicant(s) HONG ET AL.	
	Examiner CELESTE A. RONEY	Art Unit 1612	AIA (First Inventor to File) Status No

-- 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 *7/18/17*.

☐ 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) *1-10* is/are pending in the application.

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

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-10* 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 _____ 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 *7/18/17*.

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

4) ☐ Other: _____.

DETAILED ACTION

Previous Rejections

Applicants' arguments, filed 7/18/17, have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 103

The following is a quotation of pre-AIA 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, 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.

Claim 1 is rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Rahman et al (WO 2003/030864), in view of Matulic-Adamic et al (US 2002/0028919).

Rahman disclosed liposomal formulations of entrapped irinotecan, at the abstract and title. The liposomes comprised phospholipids, e.g., phosphatidylcholine, at claims 11 and 17. The compositions were useful in the treatment of cancer, at the abstract.

The compositions comprised 1-50 wt. % irinotecan and 1-95 wt. % phosphatidylcholine, at page 5 and lines 4-11. At 50 wt. % irinotecan (e.g., 0.5 ÷ 587 g/mol = 0.00085 mol) and 95 wt. % phosphatidylcholine (e.g., 0.95 ÷758 g/mol

= 0.00125 mol), Rahman's molar ratio of irinotecan to phospholipid is 0.7:1 (e.g. 0.00085 ÷ 0.00125), which falls within the instantly recited range of 0.15:1 to 1.5:1.

Rahman did not disclose triphosphate, as recited in claim 1.

Matulic-Adamic disclosed nucleotide tri-phosphates (claims 1 and 3), as liposomal encapsulated [0087] anticancer agents, at [0032],

Matulic-Adamic did not disclose irinotecan.

Since Rahman disclosed the treatment of cancer with anticancer agents generally (abstract), it would have been prima facie obvious to one of ordinary skill in the art to have incorporated nucleotide tri-phosphates within Rahman, as taught by Matulic-Adamic. The MPEP, at section 2144.07, states that generally, it is prima facie obvious to select a known material for incorporation into a composition, based on its recognized suitability for its intended use. In the instant case, it is prima facie obvious to select a nucleotide tri-phosphate compound for incorporation into a composition, based on its recognized suitability for its intended use as an anticancer agent, as taught by Matulic-Adamic.

The instant claim 1 recites a 0.15:1 to 1.5:1 molar ratio of irinotecan to phospholipid. Rahman disclosed a 0.7:1 irinotecan to phospholipid molar ratio, as discussed above. In the case where the claimed ranges "overlap or lie inside ranges disclosed by the prior art", a prima facie case of obviousness exists. MPEP 2144.05 A.

Applicant's Arguments and Examiner's Response

Applicants argued that the Office Action failed to make a prima facie case of obviousness.

The Examiner disagrees that the Office Action failed to make a prima facie case of obviousness. Rahman disclosed liposomal formulations of entrapped irinotecan for the treatment of cancer, however, Rahman did not disclose triphosphate. But, Matulic-Adamic disclosed nucleotide triphosphates as liposomal encapsulated anticancer agents.

Since Rahman disclosed the treatment of cancer with anticancer agents generally (abstract), it would have been prima facie obvious to one of ordinary skill in the art to have incorporated nucleotide tri-phosphates within Rahman, as taught by Matulic-Adamic. The MPEP, at section 2144.07, states that generally, it is prima facie obvious to select a known material for incorporation into a composition, based on its recognized suitability for its intended use. In the instant case, it is prima facie obvious to select a nucleotide tri-phosphate compound for incorporation into a composition, based on its recognized suitability for its intended use as an anticancer agent, as taught by Matulic-Adamic.

Applicants argued that the claims recite triphosphate, while Matulic-Adamic disclosed nucleotide triphosphates, wherein the triphosphate is covalently bonded to a nucleoside. Applicants argued that an ordinarily skilled artisan would know that triphphosphate and nucleotide triphosphate have very different chemical structures and biological activities.

The Examiner responds that the present claims do not exclude nucleotide triphosphates, nor do the claims excludes other components which are bound to the nucleotide. Triphosphates are not specific compounds. For example, triphosphates can be salts (e.g., sodium triphosphates), or a part of molecules (e.g., adenosine triphosphate), etc. As such, the claims are not limited to a specific compound, and thus include nucleoside triphosphates.

Applicants argued that Matulic-Adamic does not teach the use of triphosphate, nor would an ordinarily skilled artisan be motivated to create liposomal triphosphate, given only the mere suggestion of liposomal nucleoside triphosphates as disclosed in Matulic-Adamic.

The Examiner disagrees that Matulic-Adamic does not teach liposomal triphosphates, as discussed above.

Claims 2-3 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Rahman et al (WO 2003/030864), in view of Matulic-Adamic et al (US 2002/0028919) and further in view of Mentrup Edgar et al (USP 5,498,420).

The 35 U.S.C. 103(a) rejection over Rahman, in view of Matulic-Adamic has been discussed above. Additionally, Rahman disclosed, at claims 11 and 17, that the liposome forming material was phosphatidyl choline and cholesterol.

Although Rahman disclosed phosphatidyl choline as a lipid forming material, Rahman did not specifically disclose lecithin, as recited in claims 2-3.

However, Mentrup Edgar disclosed liposome vesicles comprised of phosphatidyl choline, wherein the phosphatidyl choline was in the form of a natural lecithin, at claims 1 and 5.

Mentrup Edgar did not disclose irinotecan.

Since Rahman disclosed liposomes comprised of phosphatidyl choline, it would have been prima facie obvious to one of ordinary skill in the art to have included lecithin within Rahman's composition, as taught by Mentrup Edgar. It is prima facie obvious to select lecithin for incorporation into a liposome, based on its recognized suitability for its intended use as a vesicle forming lipid, as taught by Mentrup Edgar at claims 1 and 5.

Claim 3 is rendered prima facie obvious because Rahman disclosed 1-95 wt. % of the liposome forming material (e.g., phosphatidyl choline and cholesterol), as discussed above.

At 95 wt. % phosphatidylcholine (e.g., lecithin) (e.g., 0.95 ÷758 g/mol = 0.00125 mol) and 30 wt. % cholesterol (e.g., 0.30 ÷ 387 g/mol = 0.0008 mol), Rahman's molar ratio of phosphatidyl choline (e.g., lecithin) to cholesterol is the instantly recited 3:2 (e.g. 0.00125 + 0.0008).

Applicant's Arguments and Examiner's Response

Applicants argued that claims 2-3 are dependent from claim 1, and are allowable based on dependency.

The Examiner responds that patentable subject matter has not been identified in the instant application, and as such, claims 2-3 stand rejected.

Claims 4-9 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Rahman et al (WO 2003/030864), in view of Matulic-Adamic et al (US 2002/0028919) and further in view of Ellens et al (US 2004/0013720).

The 35 U.S.C. 103(a) rejection over Rahman, in view of Matulic-Adamic has been discussed above.

Additionally, Rahman disclosed phospholipids as liposome-forming lipids, in general, at page 8 and lines 7-8.

However, Rahman did not specifically disclose DSPC, as recited in claims 4-5 and 8-9. Also, Rahman did not disclose an amphipathic polymer comprising a polyethylene glycol-lipid, as recited in claims 5-9.

Ellens disclosed liposomes as vesicular drug delivery vesicles, at the abstract. The liposomes comprised phospholipids, as vesicle forming lipids commonly known in the art; DSPC was specifically disclosed as said phospholipid, at [0023-0025].

Polyethylene glycols (PEG) (e.g., hydrophilic polymer) were disclosed to increase blood circulation times, and to provide improved delivery of the liposomes, at [0014 and 0038]. The polyethylene glycols were disclosed as methoxy-capped (e.g., mPEG), and as having a molecular weight of about 300-7,000, at [0040]. Finally, the PEG was disclosed as PEG-DSPE (e.g., mPEG-DSPE), at 0-20 mole percent, at [0082],

Ellens did not disclose a triphosphate.

Since Rahman disclosed liposomes generally comprised of phospholipids as vesicle forming lipids, it would have been prima facie obvious to one of ordinary skill in the art to have included DSPC within Rahman, as taught by Ellens. An ordinarily skilled artisan would have been motivated because DSPC is commonly known in the art as a liposome vesicle forming lipid, as taught by Ellens at [0023-0025]. Further, It is prima facie obvious to select DSPC for incorporation into a liposome, based on its recognized suitability for its intended use as a vesicle forming lipid, as taught by Ellens.

Since Rahman disclosed liposomes, it would have been prima facie obvious to one of ordinary skill in the art to have incorporated an amphipathic polymer comprising a polyethylene glycol (e.g., mPEG-DSPE) within Rahman, as taught by Ellens. An ordinarily skilled artisan would have been motivated because said polymers provide improved delivery of the liposomes, as taught by Ellens at [0014 and 0038].

Claim 4 recites DSPC and cholesterol in a 3:2 mole ratio. Rahman disclosed 1-95 wt. % of the liposome forming material (e.g., phospholipids and cholesterol), as discussed above. Ellens disclosed DSPC as a commonly known phospholipid, as discussed above.

At 95 wt. % DSPC (e.g., 0.95 ÷ 790 g/mol = 0.0012 mol) and 30 wt. % cholesterol (e.g., 0.30 ÷ 387 g/mol = 0.0008 mol), Rahman's molar ratio of phospholipid (e.g., DSPC) to cholesterol is the instantly recited 3:2 (e.g. 0.0012 ÷ 0.0008).

Claims 5-7 are rendered prima facie obvious because Ellens disclosed mPEG-DSPE having a molecular weight of 300-7,000, as discussed above.

Claim 7 recites a PEG-DSPE molecular weight of from about 250 to about 20,000. Ellens disclosed mPEG-DSPE with a molecular weight of 300-7,000. A prima facie case of obviousness exists because of overlap, as discussed above.

Claims 8-9 are rendered prima facie obvious because Rahman disclosed a 3:2 molar ratio of phospholipid to cholesterol, as discussed above. Ellens disclosed DSPC, as discussed above. Further, Ellens disclosed PEG-DSPE (e.g., mPEG-DSPE), at 0-20 mole percent, as discussed above.

Claims 8-9 recite mPEG-DSPE at 0.015 mole. Further, claim 9 recites a molecular weight of PEG of 2,000. Ellens disclosed mPEG-DSPE at 0-20 mole. Additionally, Ellens disclosed PEG having a molecular weight of 300-7,000 as discussed above. A prima facie case of obviousness exists because of overlap, as discussed above.

Applicant's Arguments and Examiner's Response

Applicants argued that claims 4-9 are dependent from claim 1, and are allowable based on dependency.

The Examiner responds that patentable subject matter has not been identified in the instant application, and as such, claims 4-9 stand rejected.

Claim 10 is rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Rahman et al (WO 2003/030864), in view of Matulic-Adamic et al (US 2002/0028919) and further in view of Abai et al (WO 1990/014074).

The 35 U.S.C. 103(a) rejection over Rahman, in view of Matulic-Adamic has been discussed above.

Additionally, Rahman disclosed that the liposomes can be formed of negatively charged lipids, at page 4 and line 34. However, Rahman did not disclose the molar amount of phospholipids, as recited in claim 10.

Abai disclosed liposomal formulations comprised of at least 1 mole percent of negatively charged phospholipids, at claim 1.

Abai did not disclose irinotecan.

Since Rahman disclosed liposomes comprised of negative phospholipids, it would have been prima facie obvious to one of ordinary skill in the art to have included said phospholipids within Rahman at the amount of 1 mole, as taught by Abai. An ordinarily skilled artisan would have been motivated to have included the phospholipid in an amount sufficient to form the liposome, as taught by Abai at claim 1. An ordinarily skilled artisan would have been motivated to have included negatively charged phospholipids within Rahman at 1 mole, because at said amount, the ingredients are vesicle forming lipids, as taught by Abai.

Claim 10 recites 132.9 g of irinotecan and 1 mole of phospholipid. Rahman disclosed 1-50 wt. % irinotecan and 1-95 wt. % phosphatidylcholine, as discussed above. At 1-50 wt. % irinotecan is 5.87-294 g (e.g., (0.01-0.5) * 587 g/mole). Abai disclosed at least 1 mole percent of a negative phospholipid. A prima facie case of obviousness exists because of overlap, as discussed above.

Applicant's Arguments and Examiner's Response

Applicants argued that claim 10 is dependent from claim 1, and is allowable based on dependency.

The Examiner responds that patentable subject matter has not been identified in the instant application, and as such, claim 10 stands rejected.

Nonstatutory Double Patenting

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 1-10 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1, 3-4, 8, 10-11 and 21-24 of copending Application No. 14/964,239, in view of Matulic-Adamic et al (US 2002/0028919).

Although the claims at issue are not identical, they are not patentably distinct from each other. The copending claims recite all of the features instantly recited for the liposome except for a triphosphate. The instant claims require a triphosphate, and such an ingredient is not recited by the copending claims.

Matulic-Adamic disclosed nucleotide tri-phosphates as liposomal encapsulated anticancer agents.

It would have been prima facie obvious to one of ordinary skill in the art to have included trip-phosphates in the copending formulation, because triphosphates are anticancer agents, as discussed above, and as taught by Matulic-Adamic.

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

Claims 1-10 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-16 of copending Application No. 14/966,458, which has issued as a U.S. Patent, in view of Matulic-Adamic et al (US 2002/0028919).

Although the claims at issue are not identical, they are not patentably distinct from each other. The issued claims recite all of the features instantly recited for the liposome except for a triphosphate. The instant claims require a triphosphate, and such an ingredient is not recited by the issued claims.

Matulic-Adamic disclosed nucleotide tri-phosphates as liposomal encapsulated anticancer agents.

It would have been prima facie obvious to one of ordinary skill in the art to have included trip-phosphates in the issued formulation, because triphosphates are anticancer agents, as discussed above, and as taught by Matulic-Adamic.

Claims 1-10 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-24 of copending Application No. 15/364,021, in view of Matulic-Adamic et al (US 2002/0028919).

Although the claims at issue are not identical, they are not patentably distinct from each other. The copending claims recite all of the features instantly recited for the liposome except for a triphosphate. The instant claims require a triphosphate, and such an ingredient is not recited by the copending claims.

Matulic-Adamic disclosed nucleotide tri-phosphates as liposomal encapsulated anticancer agents.

It would have been prima facie obvious to one of ordinary skill in the art to have included trip-phosphates in the copending formulation, because triphosphates are anticancer agents, as discussed above, and as taught by Matulic-Adamic.

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

Claims 1-10 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-19 of copending Application No. 15/363,923, in view of Matulic-Adamic et al (US 2002/0028919).

Although the claims at issue are not identical, they are not patentably distinct from each other. The copending claims recite all of the features instantly recited for the liposome except for a triphosphate. The instant claims require a triphosphate, and such an ingredient is not recited by the copending claims.

Matulic-Adamic disclosed nucleotide tri-phosphates as liposomal encapsulated anticancer agents.

It would have been prima facie obvious to one of ordinary skill in the art to have included trip-phosphates in the copending formulation, because triphosphates are anticancer agents, as discussed above, and as taught by Matulic-Adamic.

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

Claims 1-10 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-10 of copending Application No. 15/363,978, in view of Matulic-Adamic et al (US 2002/0028919).

Although the claims at issue are not identical, they are not patentably distinct from each other. The copending claims recite all of the features instantly recited for the liposome except for a triphosphate. The instant claims require a triphosphate, and such an ingredient is not recited by the copending claims.

Matulic-Adamic disclosed nucleotide tri-phosphates as liposomal encapsulated anticancer agents.

It would have been prima facie obvious to one of ordinary skill in the art to have included trip-phosphates in the copending formulation, because triphosphates are anticancer agents, as discussed above, and as taught by Matulic-Adamic.

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

Applicant's Arguments and Examiner's Response

Applicants requested that the nonstatutory obviousness-type rejections be held in abeyance until all other rejections have been overcome and the only remaining rejections are non-statutory double patenting rejections.

The Examiner responds that the nonstatutory obviousness-type rejections are not the only remaining rejections in the instant application, and as such, they are maintained.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CELESTE A. RONEY whose telephone number is (571)272-5192. The examiner can normally be reached on Monday-Thursday; 7A-5P.

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, Fred Krass can be reached on 571-272-0580. 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.

/CELESTE A. RONEY/
Examiner, Art Unit 1612

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/363,761	11/29/2016	Keelung Hong	263266-411568	1062

139696 7590 12/14/2017

Honigman Miller Schwartz and Cohn LLP/Ipsen
350 East Michigan Avenue, Suite 300
Kalamazoo, MI 49007

EXAMINER	
RONEY, CELESTE A	

ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
12/14/2017	ELECTRONIC

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

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

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

patents@honigman.com
lzerby@honigman.com
arhoades@honigman.com

Applicant-Initiated Interview Summary	Application No. 15/363,761	Applicant(s) Hong et al.	
	Examiner CELESTE A RONEY	Art Unit 1612	AIA Status No

All participants (applicant, applicants representative, PTO personnel):

(1) CELESTE A. RONEY.

(2) Christopher Forbes and Cindy Bott.

(3) Eileen Ennis.

(4) Fred Krass.

Date of Interview: 07 December 2017.

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

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

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

Claim(s) discussed: 1.

Identification of prior art discussed: Of Record.

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

Applicants argued that the irinotecan triphosphate of the instant invention is a salt, and as such, overcomes the prior art. Applicants discussed potential claim amendments to clarify that the composition is a salt. Applicants and Examiner discussed the AFCP 2.0 program as a potential path forward with claim amendments. Claim amendments will be considered upon receipt..

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

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

☐ Attachment

/CELESTE A RONEY/ Primary Examiner, Art Unit 1612	

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) 1.133 Interviews
Paragraph (b)

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

37 CFR §1.2 Business to be transacted in writing.
All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

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

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiners responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicants correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

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

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

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

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

Examiner to Check for Accuracy

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

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/363,923	11/29/2016	Keelung Hong	239669-405558/1001130US19	2163

133156 7590 02/01/2017

Honigman Miller Schwartz and Cohn LLP
350 East Michigan Avenue
Suite 300
Kalamazoo, MI 49007

EXAMINER
RONEY, CELESTE A

ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
02/01/2017	ELECTRONIC

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

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

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

patents@honigman.com
lbroecker@honigman.com
lzerby@honigman.com

Office Action Summary	Application No. 15/363,923	Applicant(s) HONG ET AL.	
	Examiner CELESTE A. RONEY	Art Unit 1612	AIA (First Inventor to File) Status No

-- 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 *11/29/16*.

☐ 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) *1-19* is/are pending in the application.

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

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-19* is/are rejected.

8)☒ Claim(s) *3* 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 _____ 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 *11/29/16 and 12/14/16*.

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

4) ☐ Other: _____.

DETAILED ACTION

Notice of Pre-AIA or AIA Status

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

Claim Objections

Claim 3 is objected to because of the following informalities: Claim 3 recites the phrase “lecithinand," which should contain a space between the words “lecithin” and “and”. Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

1. Claims 1-19 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claims do not fall within at least one of

the four categories of patent eligible subject matter because the claims are directed to compositions comprising naturally occurring substances (e.g., inositol hexaphosphate).

The claims are directed to compositions containing inositol hexaphosphate, a naturally occurring polyphosphorylated carbohydrate that is present in substantial amounts in almost all plant and mammalian cells (e.g., see Vucenik et al, J Nutr, 133, 2003, 3778S-3784S, abstract).

Inositol hexaphosphate is identified as a product of nature because this ingredient, contained in compositions thereunto, does not contain characteristics (e.g., biological or pharmacological functions or activities; chemical and physical properties; structure and form) that are markedly different than the characteristics of the ingredient as it exist in nature (e.g., plant and mammalian cells). For example, the structure, physical properties and/or function of inositol hexaphosphate is not changed just because it exists together with irinotecan in a liposome.

Because the claimed composition does not have markedly different characteristics than the ingredient as it exists in nature, the claimed composition is a “product of nature” exception. Further the claims do not include any additional features that could add significantly more to the exception. As such, the claims are ineligible under 35 USC § 101.

Claim Rejections - 35 USC § 103

The following is a quotation of pre-AIA 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, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 1 and 10 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Rahman et al (WO 2003/030864), in view of Vucenik et al (J Nutr, 133, 2003, 3778S-3784S).

Rahman disclosed liposomal formulations of entrapped irinotecan, at the abstract and title. The liposomes comprised phospholipids, e.g., phosphatidylcholine, at claims 11 and 17. The compositions were useful in the treatment of cancer, at the abstract.

The compositions comprised 1-50 wt. % irinotecan and 1-95 wt. % phosphatidylcholine, at page 5 and lines 4-11. At 50 wt. % irinotecan (e.g., 0.5 ÷ 587 g/mol = 0.00085 mol) and 95 wt. % phosphatidylcholine (e.g., 0.95 ÷ 758 g/mol = 0.00125 mol), Rahman's molar ratio of irinotecan to phospholipid is 0.7:1 (e.g. 0.00085 ÷ 0.00125), which falls within the instantly recited range of 0.15:1 to 1.5:1.

Rahman did not disclose inositol hexaphosphate, as recited in claim 1.

Vucenik disclosed that inositol hexaphosphate (IP_6) is a naturally occurring polyphosphorylated carbohydrate that is present in substantial amounts in almost all plant and mammalian cells. A striking anticancer effect of IP_6 was demonstrated. Further, in addition to reducing cell proliferation, IP_6 increases differentiation of malignant cells, often resulting in a reversion to the normal phenotype. Enhanced immunity and antioxidant properties of the drug further contribute to tumor cell destruction (abstract).

Vucenik did not disclose irinotecan.

Since Rahman disclosed the treatment of cancer with anticancer agents generally (abstract), it would have been prima facie obvious to one of ordinary skill in the art to have incorporated inositol hexaphosphate within Rahman, as taught by Vucenik. An ordinarily skilled artisan would have been motivated because inositol hexaphosphate demonstrates a striking anticancer effect by reducing cell proliferation and increasing differentiation of malignant cells, which often results in a reversion to the normal phenotype. Additionally, enhanced immunity and antioxidant properties of the drug further contribute to tumor cell destruction, as taught by Vucenik at the abstract.

The MPEP, at section 2144.07, states that generally, it is prima facie obvious to select a known material for incorporation into a composition, based on its recognized suitability for its intended use. In the instant case, it is prima facie obvious to select inositol hexaphosphate for incorporation into a composition, based on its recognized suitability for its intended use as an anticancer agent, as taught by Vucenik.

The instant claim 1 recites a 0.15:1 to 1.5:1 molar ratio of irinotecan to phospholipid. Rahman disclosed a 0.7:1 irinotecan to phospholipid molar ratio, as discussed above. In the case where the claimed ranges "overlap or lie inside ranges disclosed by the prior art", a prima facie case of obviousness exists. MPEP 2144.05 A.

Claim 10 is rendered prima facie obvious because Rahman disclosed vesicle sizes of the liposomes at about 5 µm or less (e.g., less than 5000 nm), at claim 13.

The instant claim 10 recites a liposome having a size of 104 ± 39 nm, as measured by QELS. Rahman disclosed liposomes at 5000 nm or less. Even though

product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production, or in the instant case, its method of measurement. Rahman's liposome is considered the same as or obvious from the instant liposome, and as such, claim 10 is unpatentable, even though the diameter of the instant product was measured by a different process.

The instant claim 10 recites a size of 104 ± 39 nm. Rahman disclosed sizes at 5000 nm or less. A prima facie case of obviousness exists because of overlap, as discussed above.

3. Claims 2-3 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Rahman et al (WO 2003/030864), in view of Vucenik et al (J Nutr, 133, 2003, 3778S-3784S) and further in view of Mentrup Edgar et al (USP 5,498,420).

The 35 U.S.C. 103(a) rejection over Rahman, in view of Vucenik has been discussed above. Additionally, Rahman disclosed, at claims 11 and 17, that the liposome forming material was phosphatidyl choline and cholesterol.

Although Rahman disclosed phosphatidyl choline as a lipid forming material, Rahman did not specifically disclose lecithin, as recited in claims 2-3.

However, Mentrup Edgar disclosed liposome vesicles comprised of phosphatidyl choline, wherein the phosphatidyl choline was in the form of a natural lecithin, at claims 1 and 5.

Mentrup Edgar did not disclose irinotecan.

Since Rahman disclosed liposomes comprised of phosphatidyl choline, it would have been prima facie obvious to one of ordinary skill in the art to have included lecithin within Rahman's composition, as taught by Mentrup Edgar. It is prima facie obvious to select lecithin for incorporation into a liposome, based on its recognized suitability for its intended use as a vesicle forming lipid, as taught by Mentrup Edgar at claims 1 and 5.

Claim 3 is rendered prima facie obvious because Rahman disclosed 1-95 wt. % of the liposome forming material (e.g., phosphatidyl choline and cholesterol), as discussed above.

At 95 wt. % phosphatidylcholine (e.g., lecithin) (e.g., 0.95 ÷ 758 g/mol = 0.00125 mol) and 30 wt. % cholesterol (e.g., 0.30 ÷ 387 g/mol = 0.0008 mol), Rahman's molar ratio of phosphatidyl choline (e.g., lecithin) to cholesterol is the instantly recited 3:2 (e.g. 0.00125 ÷ 0.0008).

4. Claims 4-9 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Rahman et al (WO 2003/030864), in view of Vucenik et al (J Nutr, 133, 2003, 3778S-3784S) and further in view of Ellens et al (US 2004/0013720).

The 35 U.S.C. 103(a) rejection over Rahman, in view of Vucenik has been discussed above.

Additionally, Rahman disclosed phospholipids as liposome-forming lipids, in general, at page 8 and lines 7-8.

However, Rahman did not specifically disclose DSPC, as recited in claims 4-5 and 8-9. Also, Rahman did not disclose an amphipathic polymer comprising a polyethylene glycol-lipid, as recited in claims 5-9.

Ellens disclosed liposomes as drug delivery vesicles, at the abstract. The liposomes comprised phospholipids, as vesicle forming lipids commonly known in the art; DSPC was specifically disclosed as said phospholipid, at [0023-0025].

Polyethylene glycols (PEG) (e.g., hydrophilic polymer) were disclosed to increase blood circulation times, and to provide improved delivery of the liposomes, at [0014 and 0038]. The polyethylene glycols were disclosed as methoxy-capped (e.g., mPEG), and as having a molecular weight of about 300-7,000, at [0040]. Finally, the PEG was disclosed as PEG-DSPE (e.g., mPEG-DSPE), at 0-20 mole percent, at [0082],

Ellens did not disclose inositol hexaphosphate.

Since Rahman disclosed liposomes generally comprised of phospholipids as vesicle forming lipids, it would have been prima facie obvious to one of ordinary skill in the art to have included DSPC within Rahman, as taught by Ellens. An ordinarily skilled artisan would have been motivated because DSPC is commonly known in the art as a liposome vesicle forming lipid, as taught by Ellens at [0023-0025]. Further, It is prima facie obvious to select DSPC for incorporation into a liposome, based on its recognized suitability for its intended use as a vesicle forming lipid, as taught by Ellens.

Since Rahman disclosed liposomes, it would have been prima facie obvious to one of ordinary skill in the art to have incorporated an amphipathic polymer comprising a polyethylene glycol (e.g., mPEG-DSPE) within Rahman, as taught by

Ellens. An ordinarily skilled artisan would have been motivated because said polymers provide improved delivery of the liposomes, as taught by Ellens at [0014 and 0038].

Claim 4 recites DSPC and cholesterol in a 3:2 mole ratio. Rahman disclosed 1-95 wt. % of the liposome forming material (e.g., phospholipids and cholesterol), as discussed above. Ellens disclosed DSPC as a commonly known phospholipid, as discussed above.

At 95 wt. % DSPC (e.g., 0.95 ÷ 790 g/mol = 0.0012 mol) and 30 wt. % cholesterol (e.g., 0.30 ÷ 387 g/mol = 0.0008 mol), Rahman's molar ratio of phospholipid (e.g., DSPC) to cholesterol is the instantly recited 3:2 (e.g. 0.0012 ÷ 0.0008).

Claims 5-7 are rendered prima facie obvious because Ellens disclosed mPEG-DSPE having a molecular weight of 300-7,000, as discussed above.

Claim 7 recites a PEG-DSPE molecular weight of from about 250 to about 20,000. Ellens disclosed mPEG-DSPE with a molecular weight of 300-7,000. A prima facie case of obviousness exists because of overlap, as discussed above.

Claims 8-9 are rendered prima facie obvious because Rahman disclosed a 3:2 molar ratio of phospholipid to cholesterol, as discussed above. Ellens disclosed DSPC, as discussed above. Further, Ellens disclosed PEG-DSPE (e.g., mPEG-DSPE), at 0-20 mole percent, as discussed above.

Claims 8-9 recite mPEG-DSPE at 0.015 mole. Further, claim 9 recites a molecular weight of PEG of 2,000. Ellens disclosed mPEG-DSPE at 0-20 mole. Additionally, Ellens disclosed PEG having a molecular weight of 300-7,000

as discussed above. A prima facie case of obviousness exists because of overlap, as discussed above.

5. Claims 11 and 17 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Rahman et al (WO 2003/030864), in view of Vucenik et al (J Nutr, 133, 2003, 3778S-3784S), further in view of Abai et al (WO 1990/014074) and further in view of Govindarajan et al (US 2002/0035091).

The 35 U.S.C. 103(a) rejection over Rahman, in view of Vucenik has been discussed above.

Additionally, Rahman disclosed that the composition was particularly useful in treating colon cancers, at page 6 and line 19. The liposomes can be formed of negatively charged lipids, at page 4 and line 34. The composition was a dispersion of liposomes, at page 3 and line 7. The irinotecan can be administered at 5 mg/kg of body weight of a human weighing 70 kg (e.g., 5*70 = 350 mg irinotecan), although the amount of irinotecan can be adjusted to a particular optimum dosage, at page 6, lines 23-35.

However, Rahman did not specifically disclose 500 mg irinotecan; and, Rahman did not disclose the molar amount of phospholipids, as recited in claims 11 and 17.

Abai disclosed liposomal formulations comprised of at least 1 mole percent of negatively charged phospholipids, at claim 1.

Since Rahman disclosed liposomes comprised of negative phospholipids, it would have been prima facie obvious to one of ordinary skill in the art to have

included said phospholipids within Rahman at the amount of 1 mole (e.g., 1000 mmol), as taught by Abai. An ordinarily skilled artisan would have been motivated to have included the phospholipid in an amount sufficient to form the liposome, as taught by Abai at claim 1.

An ordinarily skilled artisan would have been motivated to have included negatively charged phospholipids within Rahman at 1 mole, because at said amount, the ingredients are vesicle forming lipids, as taught by Abai.

The combination of Rahman and Abai disclosed 350 mg irinotecan (e.g., as discussed above by Rahman) per 1000 mmol phospholipid (e.g., as discussed above by Abai), or 0.35 mg/mmol (e.g., 350/1000).

The combination of Rahman and Abai did not specifically disclose 500 mg irinotecan.

Govindarajan disclosed compositions and methods for the treatment of colorectal cancer, at the abstract and title. Compositions comprised irinotecan at about 500 mg, at [0022]. Liposomes were taught at [0063].

Govindarajan did not disclose inositol hexaphosphate.

The combination of Rahman and Abai are not silent the amount of drug per mmol phospholipid, as discussed above. For example, the combination of Rahman and Abai taught 0.35 mg irinotecan per mmol phospholipid. However, the combination was not as specific the ingredients as instantly recited (e.g., 500 mg drug per mmol phospholipid).

But, Govindarajan teaches that irinotecan is useful at 500 mg, which is the amount instantly recited. This ingredient, and its amount, are recognized to have

different effects (greater or less efficacy for the treatment of colorectal cancer, as taught by Govindarajan at the abstract and title) with changing amounts used. Thus, the amount of irinotecan is recognized to be result effect. As such, result effective variables can be optimized by routine experimentation, and it would have been obvious to have optimized Rahman's irinotecan, as Rahman suggests, and as taught by Govindarajan.

The combination of Rahman, Vucenik, Abai and Govindarajan teach the claimed liposomal formulation of claims 11 and 17.

Further, claims 11 and 17 recite a liposome having a size of 104 ± 39 nm, as measured by QELS. Rahman disclosed liposomes at 5000 nm or less. Regarding the measurement of the liposomes, claims 11 and 17 are interpreted as product-by-process claims, and are not considered patentably distinct from Rahman's liposomes (e.g., see the above discussion of the rejection over claim 10).

6. Claims 12-13 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Rahman et al (WO 2003/030864), in view of Vucenik et al (J Nutr, 133, 2003, 3778S-3784S) further in view of Abai et al (WO 1990/014074), further in view of Govindarajan et al (US 2002/0035091) and further in view of Mentrup Edgar et al (USP 5,498,420).

The 35 U.S.C. 103(a) rejection over Rahman, in view of Vucenik, Abai and Govindarajan has been discussed above. Additionally, Rahman disclosed, at claims 11 and 17, that the liposome forming material was phosphatidyl choline and cholesterol.

Although Rahman disclosed phosphatidyl choline as a lipid forming material, Rahman did not specifically disclose lecithin, as recited in claims 12-13.

However, Mentrup Edgar disclosed liposome vesicles comprised of phosphatidyl choline, wherein the phosphatidyl choline was in the form of a natural lecithin, at claims 1 and 5.

Mentrup Edgar did not disclose irinotecan.

Since Rahman disclosed liposomes comprised of phosphatidyl choline, it would have been prima facie obvious to one of ordinary skill in the art to have included lecithin within Rahman's composition, as taught by Mentrup Edgar. It is prima facie obvious to select lecithin for incorporation into a liposome, based on its recognized suitability for its intended use as a vesicle forming lipid, as taught by Mentrup Edgar at claims 1 and 5.

Claim 13 is rendered prima facie obvious because Rahman disclosed 1-95 wt. % of the liposome forming material (e.g., phosphatidyl choline and cholesterol), as discussed above.

At 95 wt. % phosphatidylcholine (e.g., lecithin) (e.g., 0.95 ÷ 758 g/mol = 0.00125 mol) and 30 wt. % cholesterol (e.g., 0.30 ÷ 387 g/mol = 0.0008 mol), Rahman's molar ratio of phosphatidyl choline (e.g., lecithin) to cholesterol is the instantly recited 3:2 (e.g. 0.00125 ÷ 0.0008).

7. Claims 14-16 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Rahman et al (WO 2003/030864), in view of Vucenik et al (J Nutr,

133, 2003, 3778S-3784S), further in view of Abai et al (WO 1990/014074), further in view of Govindarajan et al (US 2002/0035091) and further in view of Ellens et al (US 2004/0013720).

The 35 U.S.C. 103(a) rejection over Rahman, in view of Vucenik, Abai and Govindarajan has been discussed above. Additionally, Rahman disclosed phospholipids as liposome-forming lipids, in general, at page 8 and lines 7-8.

However, Rahman did not specifically disclose DSPC, as recited in claims 14 and 16. Also, Rahman did not disclose an amphipathic polymer comprising a polyethylene glycol-lipid, as recited in claims 15 and 16.

Ellens disclosed liposomes as drug delivery vesicles, at the abstract. The liposomes comprised phospholipids, as vesicle forming lipids commonly known in the art; DSPC was specifically disclosed as said phospholipid, at [0023-0025].

Polyethylene glycols (PEG) (e.g., hydrophilic polymer) were disclosed to increase blood circulation times, and to provide improved delivery of the liposomes, at [0014 and 0038]. The polyethylene glycols were disclosed as methoxy-capped (e.g., mPEG), and as having a molecular weight of about 300-7,000, at [0040]. Finally, the PEG was disclosed as PEG-DSPE (e.g., mPEG-DSPE), at 0-20 mole percent, at [0082],

Ellens did not disclose inositol hexaphosphate.

Since Rahman disclosed liposomes generally comprised of phospholipids as vesicle forming lipids, it would have been prima facie obvious to one of ordinary skill in the art to have included DSPC within Rahman, as taught by Ellens. An ordinarily skilled artisan would have been motivated because DSPC is commonly known in the art

as a liposome vesicle forming lipid, as taught by Ellens at [0023-0025]. Further, It is prima facie obvious to select DSPC for incorporation into a liposome, based on its recognized suitability for its intended use as a vesicle forming lipid, as taught by Ellens.

Since Rahman disclosed liposomes, it would have been prima facie obvious to one of ordinary skill in the art to have incorporated an amphipathic polymer comprising a polyethylene glycol (e.g., mPEG-DSPE) within Rahman, as taught by Ellens. An ordinarily skilled artisan would have been motivated because said polymers provide improved delivery of the liposomes, as taught by Ellens at [0014 and 0038].

Claim 15 is rendered prima facie obvious because Ellens disclosed mPEG-DSPE having a molecular weight of 300-7,000, as discussed above.

Claim 15 recites a PEG-DSPE molecular weight of from about 250 to about 20,000. Ellens disclosed mPEG-DSPE with a molecular weight of 300-7,000. A prima facie case of obviousness exists because of overlap, as discussed above.

Claim 16 recites DSPC and cholesterol in a 3:2 mole ratio. Claim 16 recites mPEG-DSPE at 0.015 mole. Further, claim 16 recites a molecular weight of PEG of 2,000.

Rahman disclosed 1-95 wt. % of the liposome forming material (e.g., phospholipids and cholesterol), as discussed above.

At 95 wt. % DSPC (e.g., 0.95 ÷ 790 g/mol = 0.0012 mol) and 30 wt. % cholesterol (e.g., 0.30 ÷ 387 g/mol = 0.0008 mol), Rahman's molar ratio of phospholipid (e.g., DSPC) to cholesterol is the instantly recited 3:2 (e.g. 0.0012 ÷ 0.0008).

Ellens disclosed DSPC as a commonly known phospholipid, as discussed above. Further, Ellens disclosed PEG-DSPE (e.g., mPEG-DSPE), at 0-20 mole percent, as discussed above. Additionally, Ellens disclosed PEG having a molecular weight of 300-7,000 as discussed above.

A prima facie case of obviousness exists because of overlap, as discussed above.

8. Claims 18 and 19 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Rahman et al (WO 2003/030864), in view of Vucenik et al (J Nutr, 133, 2003, 3778S-3784S), further in view of Abai et al (WO 1990/014074), further in view of Govindarajan et al (US 2002/0035091) and further in view of Ellens et al (US 2004/0013720).

The 35 U.S.C. 103(a) rejection over Rahman, in view of Vucenik has been discussed above.

Additionally, Rahman disclosed phospholipids as liposome-forming lipids, in general, at page 8 and lines 7-8.

However, Rahman did not specifically disclose DSPC, as recited in claims 18-19. Also, Rahman did not disclose an amphipathic polymer comprising a polyethylene glycol-lipid, as recited in claim 19.

Ellens disclosed liposomes as drug delivery vesicles, at the abstract. The liposomes comprised phospholipids, as vesicle forming lipids commonly known in the art; DSPC was specifically disclosed as said phospholipid, at [0023-0025].

Polyethylene glycols (PEG) (e.g., hydrophilic polymer) were disclosed to increase blood circulation times, and to provide improved delivery of the liposomes, at [0014 and 0038]. The polyethylene glycols were disclosed as methoxy-capped (e.g., mPEG), and as having a molecular weight of about 300-7,000, at [0040]. Finally, the PEG was disclosed as PEG-DSPE (e.g., mPEG-DSPE), at 0-20 mole percent, at [0082],

Ellens did not disclose inositol hexaphosphate.

Since Rahman disclosed liposomes generally comprised of phospholipids as vesicle forming lipids, it would have been prima facie obvious to one of ordinary skill in the art to have included DSPC within Rahman, as taught by Ellens. An ordinarily skilled artisan would have been motivated because DSPC is commonly known in the art as a liposome vesicle forming lipid, as taught by Ellens at [0023-0025]. Further, It is prima facie obvious to select DSPC for incorporation into a liposome, based on its recognized suitability for its intended use as a vesicle forming lipid, as taught by Ellens.

Since Rahman disclosed liposomes, it would have been prima facie obvious to one of ordinary skill in the art to have incorporated an amphipathic polymer comprising a polyethylene glycol (e.g., mPEG-DSPE) within Rahman, as taught by Ellens. An ordinarily skilled artisan would have been motivated because said polymers provide improved delivery of the liposomes, as taught by Ellens at [0014 and 0038].

Claims 18-19 are rendered prima facie obvious because Rahman disclosed a 3:2 molar ratio of phospholipid to cholesterol, as discussed above. Ellens disclosed DSPC, as discussed above. Further, Ellens disclosed PEG-DSPE (e.g., mPEG-DSPE), at 0-20 mole percent, as discussed above.

Claims 18-19 recite mPEG-DSPE at 0.015 mole. Further, claim 9 recites a molecular weight of PEG of 2,000. Ellens disclosed mPEG-DSPE at 0-20 mole. Additionally, Ellens disclosed PEG having a molecular weight of 300-7,000 as discussed above. A prima facie case of obviousness exists because of overlap, as discussed above.

Nonstatutory Double Patenting

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.

9. Claims 1-19 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-20 of copending Application No. 14/964,239.

Although the claims at issue are not identical, they are not patentably distinct from each other because the species recited in the copending claims (e.g. liposome comprising irinotecan and a polyphosphorylated polyol) falls within the genus (e.g., irinotecan liposome composition) recited in the claims of the instant application, and thus read on the instant claims.

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

10. Claims 1-19 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-20 of copending Application No. 14/966,458, in view of Vucenik et al (J Nutr, 133, 2003, 3778S-3784S).

Although the claims at issue are not identical, they are not patentably distinct from each other. The copending claims recite all of the features instantly recited for the liposome except for inositol hexaphosphate. The instant claims require inositol hexaphosphate, and such an ingredient is not recited by the copending claims.

Vucenik disclosed inositol hexaphosphate as an anticancer agent.

It would have been prima facie obvious to one of ordinary skill in the art to have included inositol hexaphosphate in the copending formulation, because inositol hexaphosphate is an anticancer agent, as discussed above, and as taught by Vucenik.

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

11. Claims 1-19 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-24 of copending Application No. 15/364,021, in view of Vucenik et al (J Nutr, 133, 2003, 3778S-3784S).

Although the claims at issue are not identical, they are not patentably distinct from each other. The copending claims recite all of the features instantly recited for

the liposome except for inositol hexaphosphate. The instant claims require inositol hexaphosphate, and such an ingredient is not recited by the copending claims.

Vucenik disclosed inositol hexaphosphate as an anticancer agent.

It would have been prima facie obvious to one of ordinary skill in the art to have included inositol hexaphosphate in the copending formulation, because inositol hexaphosphate is an anticancer agent, as discussed above, and as taught by Vucenik.

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

12. Claims 1-19 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-10 of copending Application No. 15/363,761, in view of Vucenik et al (J Nutr, 133, 2003, 3778S-3784S).

Although the claims at issue are not identical, they are not patentably distinct from each other. The copending claims recite all of the features instantly recited for the liposome except for inositol hexaphosphate. The instant claims require inositol hexaphosphate, and such an ingredient is not recited by the copending claims.

Vucenik disclosed inositol hexaphosphate as an anticancer agent.

It would have been prima facie obvious to one of ordinary skill in the art to have included inositol hexaphosphate in the copending formulation, because inositol hexaphosphate is an anticancer agent, as discussed above, and as taught by Vucenik.

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

13. Claims 1-19 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-10 of copending Application No. 15/363,978, in view of Vucenik et al (J Nutr, 133, 2003, 3778S-3784S).

Although the claims at issue are not identical, they are not patentably distinct from each other. The copending claims recite all of the features instantly recited for the liposome except for inositol hexaphosphate. The instant claims require inositol hexaphosphate, and such an ingredient is not recited by the copending claims.

Vucenik disclosed inositol hexaphosphate as an anticancer agent.

It would have been prima facie obvious to one of ordinary skill in the art to have included inositol hexaphosphate in the copending formulation, because inositol hexaphosphate is an anticancer agent, as discussed above, and as taught by Vucenik.

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

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CELESTE A. RONEY whose telephone number is (571)272-5192. The examiner can normally be reached on Monday-Thursday; 7A-5P.

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, Fred Krass can be reached on 571-272-0580. 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.

/CELESTE A. RONEY/
Examiner, Art Unit 1612

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15/363,923	11/29/2016	Keelung Hong	263266-411571	2163

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Honigman Miller Schwartz and Cohn LLP/Ipsen
350 East Michigan Avenue, Suite 300
Kalamazoo, MI 49007

EXAMINER	
RONEY, CELESTE A	

ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
09/13/2017	ELECTRONIC

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

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

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

patents@honigman.com
lzerby@honigman.com
arhoades@honigman.com

Office Action Summary	Application No. 15/363,923	Applicant(s) Hong et al.	
	Examiner CELESTE A RONEY	Art Unit 1612	AIA Status No

-- 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 01 August 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) 1-19 is/are pending in the application.

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

6)☐ Claim(s) _____ is/are allowed.

7)☑ Claim(s) 1-19 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 _____ 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 8/1/17 .

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

4) ☐ Other: _____ .

DETAILED CORRESPONDENCE

Previous Rejections

Applicant's arguments, filed 8/1/17, have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-19 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claims do not fall within at least one of the four categories of patent eligible subject matter because the claims are directed to compositions comprising naturally occurring substances (e.g., inositol hexaphosphate).

The claims are directed to compositions containing inositol hexaphosphate, a naturally occurring polyphosphorylated carbohydrate that is present in substantial amounts in almost all plant and mammalian cells (e.g., see Vucenik et al, J Nutr, 133, 2003, 3778S-3784S, abstract).

Inositol hexaphosphate is identified as a product of nature because this ingredient, contained in compositions thereunto, does not contain characteristics (e.g., biological or pharmacological functions or activities; chemical and physical properties; structure and

form) that are markedly different than the characteristics of the ingredient as it exists in nature (e.g., plant and mammalian cells). For example, the structure, physical properties and/or function of inositol hexaphosphate is not changed just because it exists together with irinotecan in a liposome.

Because the claimed composition does not have markedly different characteristics than the ingredient as it exists in nature, the claimed composition is a "product of nature" exception. Further the claims do not include any additional features that could add significantly more to the exception. As such, the claims are ineligible under 35 USC § 101.

Applicant's Arguments and Examiner's Response

Applicants argued that the claimed invention does not fall within the naturally occurring substance exception of statutory subject matter as defined by MPEP 2104 because in order for a claimed invention to fall within the exception, the invention recited by the claim must fall wholly within the exception. Applicants cited MPEP 2106(III). Applicants argued that he Office Action did not offer evidence or examples showing a composition comprising every limitation recited by claim 1 as a naturally occurring substance. Applicants argued that it is not sufficient for the Office Action to note that a single element of a claim, e.g., inositol hexaphosphate, is a naturally occurring substance, but must show how the claimed invention as a whole is naturally occurring.

The Examiner responds that the claims were examined under the Markedly Different Characteristics Analysis. The markedly different characteristics analysis compares the nature-based product limitation to its naturally occurring counterpart in its natural state. If there is no naturally occurring counterpart, the comparison is made to the

closest naturally occurring counterpart. If the nature-based product is a combination (e.g., composition of liposomes, irinotecan and inositol hexaphosphate), the closest counterpart is the individual nature-based components of the combination. In the instant case, inositol hexaphosphate individually, and in combination with irinotecan and liposomes, does not result in the instant claims as a whole amounting to significantly more than the judicial exception. This is because the Applicants have not shown that inositol hexaphosphate, contained in compositions thereunto, contains characteristics (e.g., biological or pharmacological functions or activities; chemical and physical properties; structure and form) that are markedly different than the characteristics of the ingredient as it exists in nature (e.g., plant and mammalian cells). For example, the structure, physical properties and/or function of inositol hexaphosphate is not changed just because it exists together with irinotecan in a liposome.

Since at least one component of the composition recited in the instant claim 1 is identified as a natural ingredient, and since that component has not been shown to have markedly different characteristics than the ingredient in its natural state, individually or in combination with the other claimed ingredients, then the composition as a whole is identified as a nature-based product. Because the claimed composition does not have markedly different characteristics than the ingredient as it exists in nature, the claimed composition is a "product of nature" exception. Further the claims do not include any additional features that could add significantly more to the exception. As such, the claims are ineligible under 35 USC § 101.

Claim Rejections - 35 USC § 103

The following is a quotation of pre-AIA 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, 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.

Claims 1 and 10 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Rahman et al (WO 2003/030864), in view of Vucenik et al (J Nutr, 133, 2003, 3778S-3784S).

Rahman disclosed liposomal formulations of entrapped irinotecan, at the abstract and title. The liposomes comprised phospholipids, e.g., phosphatidylcholine, at claims 11 and 17. The compositions were useful in the treatment of cancer, at the abstract.

The compositions comprised 1-50 wt. % irinotecan and 1-95 wt. % phosphatidylcholine, at page 5 and lines 4-11. At 50 wt. % irinotecan (e.g., 0.5 ÷ 587 g/mol = 0.00085 mol) and 95 wt. % phosphatidylcholine (e.g., 0.95 ÷ 758 g/mol = 0.00125 mol), Rahman's molar ratio of irinotecan to phospholipid is 0.7:1 (e.g. 0.00085 ÷ 0.00125), which falls within the instantly recited range of 0.15:1 to 1.5:1.

Rahman did not disclose inositol hexaphosphate, as recited in claim 1.

Vucenik disclosed that inositol hexaphosphate (IP) is a naturally occurring polyphosphorylated carbohydrate that is present in substantial amounts in almost all plant and mammalian cells. A striking anticancer effect of IP was demonstrated. Further, in addition to reducing cell proliferation, IP increases differentiation of malignant cells, often

resulting in a reversion to the normal phenotype. Enhanced immunity and antioxidant properties of the drug further contribute to tumor cell destruction (abstract).

Vucenik did not disclose irinotecan.

Since Rahman disclosed the treatment of cancer with anticancer agents generally (abstract), it would have been prima facie obvious to one of ordinary skill in the art to have incorporated inositol hexaphosphate within Rahman, as taught by Vucenik. An ordinarily skilled artisan would have been motivated because inositol hexaphosphate demonstrates a striking anticancer effect by reducing cell proliferation and increasing differentiation of malignant cells, which often results in a reversion to the normal phenotype. Additionally, enhanced immunity and antioxidant properties of the drug further contribute to tumor cell destruction, as taught by Vucenik at the abstract.

The MPEP, at section 2144.07, states that generally, it is prima facie obvious to select a known material for incorporation into a composition, based on its recognized suitability for its intended use. In the instant case, it is prima facie obvious to select inositol hexaphosphate for incorporation into a composition, based on its recognized suitability for its intended use as an anticancer agent, as taught by Vucenik.

The instant claim 1 recites a 0.15:1 to 1.5:1 molar ratio of irinotecan to phospholipid. Rahman disclosed a 0.7:1 irinotecan to phospholipid molar ratio, as discussed above. In the case where the claimed ranges "overlap or lie inside ranges disclosed by the prior art", a prima facie case of obviousness exists. MPEP 2144.05 A.

Claim 10 is rendered prima facie obvious because Rahman disclosed vesicle sizes of the liposomes at about 5 μm or less (e.g., less than 5000 nm), at claim 13.

The instant claim 10 recites a liposome having a size of 104 ± 39 nm, as measured by QELS. Rahman disclosed liposomes at 5000 nm or less. Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production, or in the instant case, its method of measurement. Rahman's liposome is considered the same as or obvious from the instant liposome, and as such, claim 10 is unpatentable, even though the diameter of the instant product was measured by a different process.

The instant claim 10 recites a size of 104 ± 39 nm. Rahman disclosed sizes at 5000 nm or less. A prima facie case of obviousness exists because of overlap, as discussed above.

Applicant's Arguments and Examiner's Response

Applicants argued that the Office Action pointed to no guidance within either Rahman or Vucenick that would lead one having skill in the art to co-formulate irinotecan with inositol hexahosphate within a liposome.

The Examiner disagrees that Rahman does not guide an ordinarily skilled artisan to co-formulate irinotecan with another compound. At the Summary of the Invention (second paragraph), Rahman disclosed that the liposomal composition can be advantageously in conjunction with secondary therapeutic agents other than campothecins, including antineoplastics, among other active agents.

Applicants argued that in order for one having skill in the art to incorporate inositol hexaphosphate within Rahman as taught by Vucenik, one having skill in the art would

have to first select inositol hexaphosphate from the multitude of existing agents known to have anticancer properties; one would then have to choose to combine only inositol hexaphosphate rather than inositol hexaphosphate and inositol with irinotecan; one would then have to choose to co-formulate, and encapsulate within a liposome, the inositol hexaphosphate with irinotecan rather than simply administer inositol hexaphosphate as an adjuvant to the irinotecan chemotherapy, as disclosed by Vucenik. Applicants argued that there is no motivation in the cited art for one having skill in the art to ignore Vucenick's teaching of a combination of inositol hexaphosphate and inositol in favor of inositol hexaphosphate alone. Applicants argued that the Office Action used hindsight knowledge of the present invention to claim a prima facie case of obviousness and arrive at the present rejection.

The Examiner disagrees that an ordinarily skilled artisan would have to select inositol hexaphosphate from the multitude of existing agents known to have anticancer properties. This is because Vucenick clearly teaches that inositol hexaphosphate has a striking anticancer effect (abstract and title).

Regarding the co-formulation of irinotecan with other active ingredients, the Examiner responds that Rahman teaches the inclusion of secondary active agents, as discussed above. Further, the current claims do not exclude Vucenik's teachings of inositol as an anticancer agent. As such, the Examiner disagrees that an ordinarily skilled artisan would have to choose to combine only inositol hexaphosphate rather than inositol hexaphosphate and inositol, as taught by Vucenik. This is because the claims as presently recited, do not exclude additional active agents.

The Examiner disagrees that a skilled artisan would have to choose between adjuvant therapies of inositol hexaphosphate versus combination therapies of inositol hexaphosphate and irinotecan. At page 3783S, first full paragraph, Vucenik disclosed that when inositol hexaphosphate plus inositol was given in combination with chemotherapy, the side effects of chemotherapy (e.g., drop in leukocyte and platelet counts, nausea, vomiting, alopecia) were diminished and patients were able to perform their daily activities.

The Examiner disagrees that a skilled artisan would have to ignore Vucenik's teachings of a combination of inositol hexaphosphate and inositol in favor of inositol hexaphosphate alone, as alleged by the Applicants. This is because the claims do not exclude inositol as an ingredient. As such, a skilled artisan would look to the teachings of Vucenik as a whole, and would not have to ignore any of Vucenik's teachings, since Vucenik's ingredients are not excluded by the instant claims.

The Examiner disagrees that there is no motivation to combine Rahman with Vucenik. Since Rahman disclosed the treatment of cancer with anticancer agents generally (abstract), it would have been prima facie obvious to one of ordinary skill in the art to have incorporated inositol hexaphosphate within Rahman, as taught by Vucenik. An ordinarily skilled artisan would have been motivated because inositol hexaphosphate demonstrates a striking anticancer effect by reducing cell proliferation and increasing differentiation of malignant cells, which often results in a reversion to the normal phenotype. Additionally, enhanced immunity and antioxidant properties of the drug further contribute to tumor cell destruction, as taught by Vucenik at the abstract.

The MPEP, at section 2144.07, states that generally, it is prima facie obvious to select a known material for incorporation into a composition, based on its

recognized suitability for its intended use. In the instant case, it is prima facie obvious to select inositol hexaphosphate for incorporation into a composition, based on its recognized suitability for its intended use as an anticancer agent, as taught by Vucenik.

The Examiner disagrees that hindsight reasoning was used to reject the present claims. This is because Rahman clearly teaches liposomal formulations of entrapped irinotecan, for the treatment of cancer, as well as formulations that include secondary active agents, as discussed above. Meanwhile, Vucenik clearly demonstrates a striking anticancer effect of inositol hexaphosphate. As such, the claims were rejected with motivation as a rationale to combine Vucenik with Rahman. A skilled artisan would be motivated to combine Vucenik with Rahman in order to treat cancer, as taught by both Rahman and Vucenik.

The Applicants argued that the Office Action did not distinctly point out each limitation of claim 1 in the art. Applicants argued that the talents of one having ordinary skill in the art do not cure the deficiencies of the cited art.

The Examiner disagrees that the Office Action did not distinctly point out each limitation of claim 1. Claim 1 recites a pharmaceutical comprising liposomes encapsulating irinotecan and inositol hexaphosphate, wherein the liposomes comprise phospholipids, and wherein the molar ratio of irinotecan to lipid is between 0.15:1 to 1.5:1.

As stated in the Office Action, the teachings of Rahman were: liposomal formulations of entrapped irinotecan, at the abstract and title. The liposomes comprised phospholipids, e.g., phosphatidylcholine, at claims 11 and 17. The compositions comprised 1-50 wt. % irinotecan and 1-95 wt. % phosphatidylcholine, at page 5 and lines 4-11. At 50 wt. % irinotecan (e.g., 0.5 ÷ 587 g/mol = 0.00085 mol) and 95 wt. %

phosphatidylcholine (e.g., 0.95 ÷ 758 g/mol = 0.00125 mol), Rahman's molar ratio of irinotecan to phospholipid is 0.7:1 (e.g. 0.00085 ÷ 0.00125), which falls within the instantly recited range of 0.15:1 to 1.5:1.

The teachings of Vucenik were: inositol hexaphosphate as an anticancer agent (abstract).

Claims 2-3 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Rahman et al (WO 2003/030864), in view of Vucenik et al (J Nutr, 133, 2003, 3778S-3784S) and further in view of Mentrup Edgar et al (USP 5,498,420).

The 35 U.S.C. 103(a) rejection over Rahman, in view of Vucenik has been discussed above. Additionally, Rahman disclosed, at claims 11 and 17, that the liposome forming material was phosphatidyl choline and cholesterol.

Although Rahman disclosed phosphatidyl choline as a lipid forming material, Rahman did not specifically disclose lecithin, as recited in claims 2-3.

However, Mentrup Edgar disclosed liposome vesicles comprised of phosphatidyl choline, wherein the phosphatidyl choline was in the form of a natural lecithin, at claims 1 and 5.

Mentrup Edgar did not disclose irinotecan.

Since Rahman disclosed liposomes comprised of phosphatidyl choline, it would have been prima facie obvious to one of ordinary skill in the art to have included lecithin within Rahman's composition, as taught by Mentrup Edgar. It is prima facie obvious to select lecithin for incorporation into a liposome, based on its recognized suitability for its intended use as a vesicle forming lipid, as taught by Mentrup Edgar at claims 1 and 5.

Claim 3 is rendered prima facie obvious because Rahman disclosed 1-95 wt. % of the liposome forming material (e.g., phosphatidyl choline and cholesterol), as discussed above.

At 95 wt. % phosphatidylcholine (e.g., lecithin) (e.g., 0.95 ÷ 758 g/mol = 0.00125 mol) and 30 wt. % cholesterol (e.g., 0.30 387 g/mol = 0.0008 mol), Rahman's molar ratio of phosphatidyl choline (e.g., lecithin) to cholesterol is the instantly recited 3:2 (e.g. 0.00125 + 0.0008).

Claims 4-9 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Rahman et al (WO 2003/030864), in view of Vucenik et al (J Nutr, 133, 2003, 3778S-3784S) and further in view of Ellens et al (US 2004/0013720).

The 35 U.S.C. 103(a) rejection over Rahman, in view of Vucenik has been discussed above.

Additionally, Rahman disclosed phospholipids as liposome-forming lipids, in general, at page 8 and lines 7-8.

However, Rahman did not specifically disclose DSPC, as recited in claims 4-5 and 8-9. Also, Rahman did not disclose an amphipathic polymer comprising a polyethylene glycol-lipid, as recited in claims 5-9.

Ellens disclosed liposomes as drug delivery vesicles, at the abstract. The liposomes comprised phospholipids, as vesicle forming lipids commonly known in the art; DSPC was specifically disclosed as said phospholipid, at [0023-0025].

Polyethylene glycols (PEG) (e.g., hydrophilic polymer) were disclosed to increase blood circulation times, and to provide improved delivery of the liposomes, at [0014 and

0038]. The polyethylene glycols were disclosed as methoxy-capped (e.g., mPEG), and as having a molecular weight of about 300-7,000, at [0040]. Finally, the PEG was disclosed as PEG-DSPE (e.g., mPEG-DSPE), at 0-20 mole percent, at [0082].

Ellens did not disclose inositol hexaphosphate.

Since Rahman disclosed liposomes generally comprised of phospholipids as vesicle forming lipids, it would have been prima facie obvious to one of ordinary skill in the art to have included DSPC within Rahman, as taught by Ellens. An ordinarily skilled artisan would have been motivated because DSPC is commonly known in the art as a liposome vesicle forming lipid, as taught by Ellens at [0023-0025]. Further, It is prima facie obvious to select DSPC for incorporation into a liposome, based on its recognized suitability for its intended use as a vesicle forming lipid, as taught by Ellens.

Since Rahman disclosed liposomes, it would have been prima facie obvious to one of ordinary skill in the art to have incorporated an amphipathic polymer comprising a polyethylene glycol (e.g., mPEG-DSPE) within Rahman, as taught by Ellens. An ordinarily skilled artisan would have been motivated because said polymers provide improved delivery of the liposomes, as taught by Ellens at [0014 and 0038].

Claim 4 recites DSPC and cholesterol in a 3:2 mole ratio. Rahman disclosed 1-95 wt. % of the liposome forming material (e.g., phospholipids and cholesterol), as discussed above. Ellens disclosed DSPC as a commonly known phospholipid, as discussed above.

At 95 wt. % DSPC (e.g., 0.95 ÷ 790 g/mol = 0.0012 mol) and 30 wt. % cholesterol (e.g., 0.30 ÷ 387 g/mol = 0.0008 mol), Rahman's molar ratio of phospholipid (e.g., DSPC) to cholesterol is the instantly recited 3:2 (e.g. 0.0012 ÷ 0.0008).

Claims 5-7 are rendered prima facie obvious because Ellens disclosed mPEG-DSPE having a molecular weight of 300-7,000, as discussed above.

Claim 7 recites a PEG-DSPE molecular weight of from about 250 to about 20,000. Ellens disclosed mPEG-DSPE with a molecular weight of 300-7,000. A prima facie case of obviousness exists because of overlap, as discussed above.

Claims 8-9 are rendered prima facie obvious because Rahman disclosed a 3:2 molar ratio of phospholipid to cholesterol, as discussed above. Ellens disclosed DSPC, as discussed above. Further, Ellens disclosed PEG-DSPE (e.g., mPEG-DSPE), at 0-20 mole percent, as discussed above.

Claims 8-9 recite mPEG-DSPE at 0.015 mole. Further, claim 9 recites a molecular weight of PEG of 2,000. Ellens disclosed mPEG-DSPE at 0-20 mole. Additionally, Ellens disclosed PEG having a molecular weight of 300-7,000 as discussed above. A prima facie case of obviousness exists because of overlap, as discussed above.

Claims 11 and 17 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Rahman et al (WO 2003/030864), in view of Vucenik et al (J Nutr, 133, 2003, 3778S-3784S), further in view of Abai et al (WO 1990/014074) and further in view of Govindarajan et al (US 2002/0035091).

The 35 U.S.C. 103(a) rejection over Rahman, in view of Vucenik has been discussed above.

Additionally, Rahman disclosed that the composition was particularly useful in treating colon cancers, at page 6 and line 19. The liposomes can be formed of negatively charged lipids, at page 4 and line 34. The composition was a dispersion of liposomes, at

page 3 and line 7. The irinotecan can be administered at 5 mg/kg of body weight of a human weighing 70 kg (e.g., 5*70 = 350 mg irinotecan), although the amount of irinotecan can be adjusted to a particular optimum dosage, at page 6, lines 23-35.

However, Rahman did not specifically disclose 500 mg irinotecan; and, Rahman did not disclose the molar amount of phospholipids, as recited in claims 11 and 17.

Abai disclosed liposomal formulations comprised of at least 1 mole percent of negatively charged phospholipids, at claim 1.

Since Rahman disclosed liposomes comprised of negative phospholipids, it would have been prima facie obvious to one of ordinary skill in the art to have included said phospholipids within Rahman at the amount of 1 mole (e.g., 1000 mmol), as taught by Abai. An ordinarily skilled artisan would have been motivated to have included the phospholipid in an amount sufficient to form the liposome, as taught by Abai at claim 1.

An ordinarily skilled artisan would have been motivated to have included negatively charged phospholipids within Rahman at 1 mole, because at said amount, the ingredients are vesicle forming lipids, as taught by Abai.

The combination of Rahman and Abai disclosed 350 mg irinotecan (e.g., as discussed above by Rahman) per 1000 mmol phospholipid (e.g., as discussed above by Abai), or 0.35 mg/mmol (e.g., 350/1000).

The combination of Rahman and Abai did not specifically disclose 500 mg irinotecan.

Govindarajan disclosed compositions and methods for the treatment of colorectal cancer, at the abstract and title. Compositions comprised irinotecan at about 500 mg, at [0022]. Liposomes were taught at [0063].

Govindarajan did not disclose inositol hexaphosphate.

The combination of Rahman and Abai are not silent the amount of drug per mmol phospholipid, as discussed above. For example, the combination of Rahman and Abai taught 0.35 mg irinotecan per mmol phospholipid. However, the combination was not as specific the ingredients as instantly recited (e.g., 500 mg drug per mmol phospholipid).

But, Govindarajan teaches that irinotecan is useful at 500 mg, which is the amount instantly recited. This ingredient, and its amount, are recognized to have different effects (greater or less efficacy for the treatment of colorectal cancer, as taught by Govindarajan at the abstract and title) with changing amounts used. Thus, the amount of irinotecan is recognized to be result effect. As such, result effective variables can be optimized by routine experimentation, and it would have been obvious to have optimized Rahman's irinotecan, as Rahman suggests, and as taught by Govindarajan.

The combination of Rahman, Vucenik, Abai and Govindarajan teach the claimed liposomal formulation of claims 11 and 17.

Further, claims 11 and 17 recite a liposome having a size of 104 ± 39 nm, as measured by QELS. Rahman disclosed liposomes at 5000 nm or less. Regarding the measurement of the liposomes, claims 11 and 17 are interpreted as product-by-process claims, and are not considered patentably distinct from Rahman's liposomes (e.g., see the above discussion of the rejection over claim 10).

Claims 12-13 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Rahman et al (WO 2003/030864), in view of Vucenik et al (J Nutr, 133, 2003, 3778S-

3784S) further in view of Abai et al (WO 1990/014074), further in view of Govindarajan et al (US 2002/0035091) and further in view of Mentrup Edgar et al (USP 5,498,420).

The 35 U.S.C. 103(a) rejection over Rahman, in view of Vucenik, Abai and Govindarajan has been discussed above. Additionally, Rahman disclosed, at claims 11 and 17, that the liposome forming material was phosphatidyl choline and cholesterol.

Although Rahman disclosed phosphatidyl choline as a lipid forming material, Rahman did not specifically disclose lecithin, as recited in claims 12-13.

However, Mentrup Edgar disclosed liposome vesicles comprised of phosphatidyl choline, wherein the phosphatidyl choline was in the form of a natural lecithin, at claims 1 and 5.

Mentrup Edgar did not disclose irinotecan.

Since Rahman disclosed liposomes comprised of phosphatidyl choline, it would have been prima facie obvious to one of ordinary skill in the art to have included lecithin within Rahman's composition, as taught by Mentrup Edgar. It is prima facie obvious to select lecithin for incorporation into a liposome, based on its recognized suitability for its intended use as a vesicle forming lipid, as taught by Mentrup Edgar at claims 1 and 5.

Claim 13 is rendered prima facie obvious because Rahman disclosed 1-95 wt. % of the liposome forming material (e.g., phosphatidyl choline and cholesterol), as discussed above.

At 95 wt. % phosphatidylcholine (e.g., lecithin) (e.g., 0.95 ÷ 758 g/mol = 0.00125 mol) and 30 wt. % cholesterol (e.g., 0.30 ÷ 387 g/mol = 0.0008 mol), Rahman's molar ratio of phosphatidyl choline (e.g., lecithin) to cholesterol is the instantly recited 3:2 (e.g. 0.00125 + 0.0008).

Claims 14-16 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Rahman et al (WO 2003/030864), in view of Vucenik et al (J Nutr, 133, 2003, 3778S-3784S), further in view of Abai et al (WO 1990/014074), further in view of Govindarajan et al (US 2002/0035091) and further in view of Ellens et al (US 2004/0013720).

The 35 U.S.C. 103(a) rejection over Rahman, in view of Vucenik, Abai and Govindarajan has been discussed above. Additionally, Rahman disclosed phospholipids as liposome-forming lipids, in general, at page 8 and lines 7-8.

However, Rahman did not specifically disclose DSPC, as recited in claims 14 and 16. Also, Rahman did not disclose an amphipathic polymer comprising a polyethylene glycol-lipid, as recited in claims 15 and 16.

Ellens disclosed liposomes as drug delivery vesicles, at the abstract. The liposomes comprised phospholipids, as vesicle forming lipids commonly known in the art; DSPC was specifically disclosed as said phospholipid, at [0023-0025].

Polyethylene glycols (PEG) (e.g., hydrophilic polymer) were disclosed to increase blood circulation times, and to provide improved delivery of the liposomes, at [0014 and 0038]. The polyethylene glycols were disclosed as methoxy-capped (e.g., mPEG), and as having a molecular weight of about 300-7,000, at [0040]. Finally, the PEG was disclosed as PEG-DSPE (e.g., mPEG-DSPE), at 0-20 mole percent, at [0082].

Ellens did not disclose inositol hexaphosphate.

Since Rahman disclosed liposomes generally comprised of phospholipids as vesicle forming lipids, it would have been prima facie obvious to one of ordinary skill in the art to have included DSPC within Rahman, as taught by Ellens. An ordinarily skilled artisan would have been motivated because DSPC is commonly known in the art as a

liposome vesicle forming lipid, as taught by Ellens at [0023-0025]. Further, It is prima facie obvious to select DSPC for incorporation into a liposome, based on its recognized suitability for its intended use as a vesicle forming lipid, as taught by Ellens.

Since Rahman disclosed liposomes, it would have been prima facie obvious to one of ordinary skill in the art to have incorporated an amphipathic polymer comprising a polyethylene glycol (e.g., mPEG-DSPE) within Rahman, as taught by Ellens. An ordinarily skilled artisan would have been motivated because said polymers provide improved delivery of the liposomes, as taught by Ellens at [0014 and 0038].

Claim 15 is rendered prima facie obvious because Ellens disclosed mPEG-DSPE having a molecular weight of 300-7,000, as discussed above.

Claim 15 recites a PEG-DSPE molecular weight of from about 250 to about 20,000. Ellens disclosed mPEG-DSPE with a molecular weight of 300-7,000. A prima facie case of obviousness exists because of overlap, as discussed above.

Claim 16 recites DSPC and cholesterol in a 3:2 mole ratio. Claim 16 recites mPEG-DSPE at 0.015 mole. Further, claim 16 recites a molecular weight of PEG of 2,000.

Rahman disclosed 1-95 wt. % of the liposome forming material (e.g., phospholipids and cholesterol), as discussed above.

At 95 wt. % DSPC (e.g., 0.95 ÷ 790 g/mol = 0.0012 mol) and 30 wt. % cholesterol (e.g., 0.30 ÷ 387 g/mol = 0.0008 mol), Rahman's molar ratio of phospholipid (e.g., DSPC) to cholesterol is the instantly recited 3:2 (e.g. 0.0012 ÷0.0008).

Ellens disclosed DSPC as a commonly known phospholipid, as discussed above. Further, Ellens disclosed PEG-DSPE (e.g., mPEG-DSPE), at 0-20 mole percent,

as discussed above. Additionally, Ellens disclosed PEG having a molecular weight of 300-7,000 as discussed above.

A prima facie case of obviousness exists because of overlap, as discussed above.

Claims 18 and 19 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Rahman et al (WO 2003/030864), in view of Vucenik et al (J Nutr, 133, 2003, 3778S-3784S), further in view of Abai et al (WO 1990/014074), further in view of Govindarajan et al (US 2002/0035091) and further in view of Ellens et al (US 2004/0013720).

The 35 U.S.C. 103(a) rejection over Rahman, in view of Vucenik has been discussed above.

Additionally, Rahman disclosed phospholipids as liposome-forming lipids, in general, at page 8 and lines 7-8.

However, Rahman did not specifically disclose DSPC, as recited in claims 18-19. Also, Rahman did not disclose an amphipathic polymer comprising a polyethylene glycol-lipid, as recited in claim 19.

Ellens disclosed liposomes as drug delivery vesicles, at the abstract. The liposomes comprised phospholipids, as vesicle forming lipids commonly known in the art; DSPC was specifically disclosed as said phospholipid, at [0023-0025].

Polyethylene glycols (PEG) (e.g., hydrophilic polymer) were disclosed to increase blood circulation times, and to provide improved delivery of the liposomes, at [0014 and 0038]. The polyethylene glycols were disclosed as methoxy-capped (e.g., mPEG), and

as having a molecular weight of about 300-7,000, at [0040]. Finally, the PEG was disclosed as PEG-DSPE (e.g., mPEG-DSPE), at 0-20 mole percent, at [0082].

Ellens did not disclose inositol hexaphosphate.

Since Rahman disclosed liposomes generally comprised of phospholipids as vesicle forming lipids, it would have been prima facie obvious to one of ordinary skill in the art to have included DSPC within Rahman, as taught by Ellens. An ordinarily skilled artisan would have been motivated because DSPC is commonly known in the art as a liposome vesicle forming lipid, as taught by Ellens at [0023-0025]. Further, It is prima facie obvious to select DSPC for incorporation into a liposome, based on its recognized suitability for its intended use as a vesicle forming lipid, as taught by Ellens.

Since Rahman disclosed liposomes, it would have been prima facie obvious to one of ordinary skill in the art to have incorporated an amphipathic polymer comprising a polyethylene glycol (e.g., mPEG-DSPE) within Rahman, as taught by Ellens. An ordinarily skilled artisan would have been motivated because said polymers provide improved delivery of the liposomes, as taught by Ellens at [0014 and 0038].

Claims 18-19 are rendered prima facie obvious because Rahman disclosed a 3:2 molar ratio of phospholipid to cholesterol, as discussed above. Ellens disclosed DSPC, as discussed above. Further, Ellens disclosed PEG-DSPE (e.g., mPEG-DSPE), at 0-20 mole percent, as discussed above.

Claims 18-19 recite mPEG-DSPE at 0.015 mole. Further, claim 9 recites a molecular weight of PEG of 2,000. Ellens disclosed mPEG-DSPE at 0-20 mole. Additionally, Ellens disclosed PEG having a molecular weight of 300-7,000 as discussed above. A prima facie case of obviousness exists because of overlap, as discussed above.

Applicant's Arguments and Examiner's Response

Applicants argued that claims 2-19 are patentable in view of the fact that claim 1 is patentable.

The Examiner disagrees that claim 1 is patentable over Rahman and Vucenik, as discussed above. As such, claims 2-19 are not patentable. Because patentable subject matter has not been identified in the present application, the rejections over claims 2-19 are maintained.

Nonstatutory Double Patenting

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 1-19 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-4, 8 and 10-11 of copending Application No. 14/964,239.

Although the claims at issue are not identical, they are not patentably distinct from each other because the species recited in the copending claims (e.g. liposome comprising irinotecan and a polyphosphorylated polyol) falls within the genus (e.g., irinotecan liposome composition) recited in the claims of the instant application, and thus read on the instant claims.

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

Claims 1-19 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-4, 5-11 and 17-20 of copending Application No. 14/966,458, which has issued as a U.S. Patent, in view of Vucenik et al (J Nutr, 133, 2003, 3778S-3784S).

Although the claims at issue are not identical, they are not patentably distinct from each other. The issued claims recite all of the features instantly recited for the liposome except for inositol hexaphosphate. The instant claims require inositol hexaphosphate, and such an ingredient is not recited by the issued claims.

Vucenik disclosed inositol hexaphosphate as an anticancer agent.

It would have been prima facie obvious to one of ordinary skill in the art to have included inositol hexaphosphate in the issued formulation, because inositol hexaphosphate is an anticancer agent, as discussed above, and as taught by Vucenik.

Claims 1-19 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-24 of copending Application No. 15/364,021, in view of Vucenik et al (J Nutr, 133, 2003, 3778S-3784S).

Although the claims at issue are not identical, they are not patentably distinct from each other. The copending claims recite all of the features instantly recited for the liposome except for inositol hexaphosphate. The instant claims require inositol hexaphosphate, and such an ingredient is not recited by the copending claims.

Vucenik disclosed inositol hexaphosphate as an anticancer agent.

It would have been prima facie obvious to one of ordinary skill in the art to have included inositol hexaphosphate in the copending formulation, because inositol hexaphosphate is an anticancer agent, as discussed above, and as taught by Vucenik.

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

Claims 1-19 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-10 of copending Application No. 15/363,761, in view of Vucenik et al (J Nutr, 133, 2003, 3778S-3784S).

Although the claims at issue are not identical, they are not patentably distinct from each other. The copending claims recite all of the features instantly recited for the liposome except for inositol hexaphosphate. The instant claims require inositol hexaphosphate, and such an ingredient is not recited by the copending claims.

Vucenik disclosed inositol hexaphosphate as an anticancer agent.

It would have been prima facie obvious to one of ordinary skill in the art to have included inositol hexaphosphate in the copending formulation, because inositol hexaphosphate is an anticancer agent, as discussed above, and as taught by Vucenik.

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

Claims 1-19 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-10 of copending Application No. 15/363,978, in view of Vucenik et al (J Nutr, 133, 2003, 3778S-3784S).

Although the claims at issue are not identical, they are not patentably distinct from each other. The copending claims recite all of the features instantly recited for the liposome except for inositol hexaphosphate. The instant claims require inositol hexaphosphate, and such an ingredient is not recited by the copending claims.

Vucenik disclosed inositol hexaphosphate as an anticancer agent.

It would have been prima facie obvious to one of ordinary skill in the art to have included inositol hexaphosphate in the copending formulation, because inositol hexaphosphate is an anticancer agent, as discussed above, and as taught by Vucenik.

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

Applicant's Arguments and Examiner's Response

Applicants requested that the non-obviousness type double patenting rejections be held in abeyance until all other rejections have been overcome, and the only remaining rejections are non-statutory double patenting rejections.

The Examiner responds that the nonstatutory double patenting rejections are not the only remaining rejections in the application, and as such, the double patenting rejections are maintained.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CELESTE A RONEY whose telephone number is (571)272-5192. The examiner can normally be reached on Monday-Thursday; 7 AM-5 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, Frederick Krass can be reached on 571-272-0580. 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.

/CELESTE A RONEY/
Examiner, Art Unit 1612

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/363,978	11/29/2016	Keelung Hong	239669-405559/1001130US20	5428

133156 7590 02/07/2017

Honigman Miller Schwartz and Cohn LLP
350 East Michigan Avenue
Suite 300
Kalamazoo, MI 49007

EXAMINER	
RONEY, CELESTE A	

ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
02/07/2017	ELECTRONIC

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

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

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

patents@honigman.com
lbroecker@honigman.com
lzerby@honigman.com

Office Action Summary	Application No. 15/363,978	Applicant(s) HONG ET AL.	
	Examiner CELESTE A. RONEY	Art Unit 1612	AIA (First Inventor to File) Status No

-- 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 *11/29/16*.

☐ 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) _____ is/are pending in the application.

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

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-10* 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 _____ 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 *11/29/16*.

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

4) ☐ Other: _____.

DETAILED ACTION

Notice of Pre-AIA or AIA Status

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

Claim Rejections - 35 USC § 103

The following is a quotation of pre-AIA 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, 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.

Claim 1 is rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Rahman et al (WO 2003/030864), in view of Vucenik et al (J Nutr, 133, 2003, 3778S-3784S) as evidenced by of Nicolau et al (WO 2003/092700).

Rahman disclosed liposomal formulations of entrapped irinotecan, at the abstract and title. The liposomes comprised phospholipids, e.g., phosphatidylcholine, at claims 11 and 17. The compositions were useful in the treatment of cancer, at the abstract.

The compositions comprised 1-50 wt. % irinotecan and 1-95 wt. % phosphatidylcholine, at page 5 and lines 4-11. At 50 wt. % irinotecan (e.g., 0.5 ÷ 587 g/mol = 0.00085 mol) and 95 wt. % phosphatidylcholine (e.g., 0.95 ÷ 758 g/mol = 0.00125 mol), Rahman's molar ratio of irinotecan to phospholipid is 0.7:1 (e.g. 0.00085 ÷ 0.00125), which falls within the instantly recited range of 0.15:1 to 1.5:1.

Rahman did not disclose pyrophosphate, as recited in claim 1.

Vucenik disclosed that inositol hexaphosphate (IP6) has a striking anticancer effect. Further, in addition to reducing cell proliferation, IP6 increases differentiation of malignant cells, often resulting in a reversion to the normal phenotype. Enhanced immunity and antioxidant properties of the drug further contribute to tumor cell destruction (abstract).

Vucenik did not disclose irinotecan.

Nicolau evidenced that inositol hexaphosphates are inositol pyrophosphates, which are compounds comprising internal pyrophosphates (Nicolau, at the title and abstract).

Since Rahman disclosed the treatment of cancer with anticancer agents generally (abstract), it would have been prima facie obvious to one of ordinary skill in the art to have incorporated inositol hexaphosphate within Rahman, as taught by Vucenik. An ordinarily skilled artisan would have been motivated because inositol hexaphosphate demonstrates a striking anticancer effect by reducing cell proliferation and increasing differentiation of malignant cells, which often results in a reversion to the normal phenotype. Additionally, enhanced immunity and antioxidant

properties of the drug further contribute to tumor cell destruction, as taught by Vucenik at the abstract.

The MPEP, at section 2144.07, states that generally, it is prima facie obvious to select a known material for incorporation into a composition, based on its recognized suitability for its intended use. In the instant case, it is prima facie obvious to select inositol hexaphosphate for incorporation into a composition, based on its recognized suitability for its intended use as an anticancer agent, as taught by Vucenik.

The instant claim 1 recites a 0.15:1 to 1.5:1 molar ratio of irinotecan to phospholipid. Rahman disclosed a 0.7:1 irinotecan to phospholipid molar ratio, as discussed above. In the case where the claimed ranges "overlap or lie inside ranges disclosed by the prior art", a prima facie case of obviousness exists. MPEP 2144.05 A.

Claim 1 recites compositions comprising pyrophosphates. Vucenik disclosed compositions comprising inositol hexaphosphate. Nicolau evidenced that inositol hexaphosphate contains an internal pyrophosphate. Therefore, it appears that the compositions of the instant claims and those of the prior art would reasonably be expected to have substantially the same physical and chemical properties. This is because the claims recite a pyrophosphate, and Vucenik teaches inositol hexaphosphate, which has an internal pyrophosphate, as evidenced by Nicolau.

Claims 2-3 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Rahman et al (WO 2003/030864), in view of Vucenik et al (J Nutr, 133, 2003,

3778S-3784S) and further in view of Mentrup Edgar et al (USP 5,498,420), as evidenced by of Nicolau et al (WO 2003/092700).

The 35 U.S.C. 103(a) rejection over Rahman, in view of Vucenik and as evidenced by Nicolau, has been discussed above. Additionally, Rahman disclosed, at claims 11 and 17, that the liposome forming material was phosphatidyl choline and cholesterol.

Although Rahman disclosed phosphatidyl choline as a lipid forming material, Rahman did not specifically disclose lecithin, as recited in claims 2-3.

However, Mentrup Edgar disclosed liposome vesicles comprised of phosphatidyl choline, wherein the phosphatidyl choline was in the form of a natural lecithin, at claims 1 and 5.

Mentrup Edgar did not disclose irinotecan.

Since Rahman disclosed liposomes comprised of phosphatidyl choline, it would have been prima facie obvious to one of ordinary skill in the art to have included lecithin within Rahman's composition, as taught by Mentrup Edgar. It is prima facie obvious to select lecithin for incorporation into a liposome, based on its recognized suitability for its intended use as a vesicle forming lipid, as taught by Mentrup Edgar at claims 1 and 5.

Claim 3 is rendered prima facie obvious because Rahman disclosed 1-95 wt. % of the liposome forming material (e.g., phosphatidyl choline and cholesterol), as discussed above.

At 95 wt. % phosphatidylcholine (e.g., lecithin) (e.g., 0.95 ÷ 758 g/mol = 0.00125 mol) and 30 wt. % cholesterol (e.g., 0.30 ÷ 387 g/mol = 0.0008 mol), Rahman's molar

ratio of phosphatidyl choline (e.g., lecithin) to cholesterol is the instantly recited 3:2 (e.g. 0.00125 ÷ 0.0008).

Claims 4-9 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Rahman et al (WO 2003/030864), in view of Vucenik et al (J Nutr, 133, 2003, 3778S-3784S) and further in view of Ellens et al (US 2004/0013720) as evidenced by of Nicolau et al (WO 2003/092700).

The 35 U.S.C. 103(a) rejection over Rahman, in view of Vucenik has been discussed above.

Additionally, Rahman disclosed phospholipids as liposome-forming lipids, in general, at page 8 and lines 7-8.

However, Rahman did not specifically disclose DSPC, as recited in claims 4-5 and 8-9. Also, Rahman did not disclose an amphipathic polymer comprising a polyethylene glycol-lipid, as recited in claims 5-9.

Ellens disclosed liposomes as drug delivery vesicles, at the abstract. The liposomes comprised phospholipids, as vesicle forming lipids commonly known in the art; DSPC was specifically disclosed as said phospholipid, at [0023-0025].

Polyethylene glycols (PEG) (e.g., hydrophilic polymer) were disclosed to increase blood circulation times, and to provide improved delivery of the liposomes, at [0014 and 0038]. The polyethylene glycols were disclosed as methoxy-capped (e.g., mPEG), and as having a molecular weight of about 300-7,000, at [0040]. Finally, the PEG was disclosed as PEG-DSPE (e.g., mPEG-DSPE), at 0-20 mole percent, at [0082],

Ellens did not disclose pyrophosphate.

Since Rahman disclosed liposomes generally comprised of phospholipids as vesicle forming lipids, it would have been prima facie obvious to one of ordinary skill in the art to have included DSPC within Rahman, as taught by Ellens. An ordinarily skilled artisan would have been motivated because DSPC is commonly known in the art as a liposome vesicle forming lipid, as taught by Ellens at [0023-0025]. Further, It is prima facie obvious to select DSPC for incorporation into a liposome, based on its recognized suitability for its intended use as a vesicle forming lipid, as taught by Ellens.

Since Rahman disclosed liposomes, it would have been prima facie obvious to one of ordinary skill in the art to have incorporated an amphipathic polymer comprising a polyethylene glycol (e.g., mPEG-DSPE) within Rahman, as taught by Ellens. An ordinarily skilled artisan would have been motivated because said polymers provide improved delivery of the liposomes, as taught by Ellens at [0014 and 0038].

Claim 4 recites DSPC and cholesterol in a 3:2 mole ratio. Rahman disclosed 1-95 wt. % of the liposome forming material (e.g., phospholipids and cholesterol), as discussed above. Ellens disclosed DSPC as a commonly known phospholipid, as discussed above.

At 95 wt. % DSPC (e.g., 0.95 ÷ 790 g/mol = 0.0012 mol) and 30 wt. % cholesterol (e.g., 0.30 ÷ 387 g/mol = 0.0008 mol), Rahman's molar ratio of phospholipid (e.g., DSPC) to cholesterol is the instantly recited 3:2 (e.g. 0.0012 ÷ 0.0008).

Claims 5-7 are rendered prima facie obvious because Ellens disclosed mPEG-DSPE having a molecular weight of 300-7,000, as discussed above.

Claim 7 recites a PEG-DSPE molecular weight of from about 250 to about 20,000. Ellens disclosed mPEG-DSPE with a molecular weight of 300-7,000. A prima facie case of obviousness exists because of overlap, as discussed above.

Claims 8-9 are rendered prima facie obvious because Rahman disclosed a 3:2 molar ratio of phospholipid to cholesterol, as discussed above. Ellens disclosed DSPC, as discussed above. Further, Ellens disclosed PEG-DSPE (e.g., mPEG-DSPE), at 0-20 mole percent, as discussed above.

Claims 8-9 recite mPEG-DSPE at 0.015 mole. Further, claim 9 recites a molecular weight of PEG of 2,000. Ellens disclosed mPEG-DSPE at 0-20 mole. Additionally, Ellens disclosed PEG having a molecular weight of 300-7,000 as discussed above. A prima facie case of obviousness exists because of overlap, as discussed above.

Claim 10 is rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Rahman et al (WO 2003/030864), in view of Vucenik et al (J Nutr, 133, 2003, 3778S-3784S) and further in view of Abai et al (WO 1990/014074) as evidenced by of Nicolau et al (WO 2003/092700).

The 35 U.S.C. 103(a) rejection over Rahman, in view of Vucenik has been discussed above.

Rahman disclosed 1-50 wt. % of irinotecan, as discussed above. At 1 wt. % irinotecan, the composition contained 5.87 g irinotecan (e.g., 0.01 * 587 g/mol = 5.87 g); at 50 wt. % irinotecan, the composition contained 293 g irinotecan (e.g., 0.5 * 587 g/mol

= 293 g). As such, Rahman disclosed compositions containing from 5.87 to 293 g of irinotecan.

Additionally, Rahman disclosed that the liposomes can be formed of negatively charged lipids, at page 4 and line 34.

However, Rahman did not specifically disclose the molar amount of phospholipids, as recited in claims 11 and 17.

Abai disclosed liposomal formulations comprised of at least 1 mole percent of negatively charged phospholipids, at claim 1.

Abai did not disclose pyrophosphate.

Since Rahman disclosed liposomes comprised of negative phospholipids, it would have been prima facie obvious to one of ordinary skill in the art to have included said phospholipids within Rahman at the amount of 1 mole, as taught by Abai. An ordinarily skilled artisan would have been motivated to have included the phospholipid in an amount sufficient to form the liposome, as taught by Abai at claim 1.

An ordinarily skilled artisan would have been motivated to have included negatively charged phospholipids within Rahman at 1 mole, because at said amount, the ingredients are vesicle forming lipids, as taught by Abai.

The combination of Rahman and Abai disclosed 5.87-293 g irinotecan (e.g., as discussed above by Rahman) per 1 mole phospholipid.

The instant claim 10 recites 136.2 g irinotecan per 1 mole of phospholipid. Rahman disclosed 5.87-293 g irinotecan. Abai disclosed 1 mole of phospholipid. A prima facie case of obviousness exists because of overlap, as discussed above.

Nonstatutory Double Patenting

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 1-10 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-20 of copending Application No. 14/964,239.

Although the claims at issue are not identical, they are not patentably distinct from each other because the species recited in the copending claims (e.g. liposome comprising irinotecan and a polyphosphorylated polyol) falls within the genus (e.g., irinotecan liposome composition) recited in the claims of the instant application, and thus read on the instant claims.

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

Claims 1-10 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-20 of copending Application

No. 14/966,458, in view of Vucenik et al (J Nutr, 133, 2003, 3778S-3784S) as evidenced by of Nicolau et al (WO 2003/092700).

Although the claims at issue are not identical, they are not patentably distinct from each other. The copending claims recite all of the features instantly recited for the liposome except for pyrophosphate. The instant claims require pyrophosphate, and such an ingredient is not recited by the copending claims.

Vucenik disclosed inositol hexaphosphate as an anticancer agent. Nicolau evidenced that inositol hexaphosphates are inositol pyrophosphates, which are compounds comprising internal pyrophosphates (Nicolau, at the title and abstract).

It would have been prima facie obvious to one of ordinary skill in the art to have included inositol hexaphosphate in the copending formulation, because inositol hexaphosphate is an anticancer agent, as discussed above, and as taught by Vucenik.

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

Claims 1-10 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-24 of copending Application No. 15/364,021, in view of Vucenik et al (J Nutr, 133, 2003, 3778S-3784S) as evidenced by of Nicolau et al (WO 2003/092700).

Although the claims at issue are not identical, they are not patentably distinct from each other. The copending claims recite all of the features instantly recited for the

liposome except for pyrophosphate. The instant claims require pyrophosphate, and such an ingredient is not recited by the copending claims.

Vucenik disclosed inositol hexaphosphate as an anticancer agent. Nicolau evidenced that inositol hexaphosphates are inositol pyrophosphates, which are compounds comprising internal pyrophosphates (Nicolau, at the title and abstract).

It would have been prima facie obvious to one of ordinary skill in the art to have included inositol hexaphosphate in the copending formulation, because inositol hexaphosphate is an anticancer agent, as discussed above, and as taught by Vucenik.

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

Claims 1-10 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-10 of copending Application No. 15/363,761, in view of Vucenik et al (J Nutr, 133, 2003, 3778S-3784S) as evidenced by of Nicolau et al (WO 2003/092700).

Although the claims at issue are not identical, they are not patentably distinct from each other. The copending claims recite all of the features instantly recited for the liposome except for pyrophosphate. The instant claims require pyrophosphate, and such an ingredient is not recited by the copending claims.

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It would have been prima facie obvious to one of ordinary skill in the art to have included inositol hexaphosphate in the copending formulation, because inositol hexaphosphate is an anticancer agent, as discussed above, and as taught by Vucenik.

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

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CELESTE A. RONEY whose telephone number is (571)272-5192. The examiner can normally be reached on Monday-Thursday; 7A-5P.

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, Fred Krass can be reached on 571-272-0580. 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.

/CELESTE A. RONEY/
Examiner, Art Unit 1612

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/363,978	11/29/2016	Keelung Hong	263266-411574	5428

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Honigman Miller Schwartz and Cohn LLP/Ipsen
350 East Michigan Avenue, Suite 300
Kalamazoo, MI 49007

EXAMINER	
RONEY, CELESTE A	

ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
08/21/2017	ELECTRONIC

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

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

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

patents@honigman.com
lzerby@honigman.com
anelson@honigman.com

Office Action Summary	Application No. 15/363,978	Applicant(s) Hong et al.	
	Examiner CELESTE A RONEY	Art Unit 1612	AIA Status No

-- 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 07 July 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) 1-10 is/are pending in the application.

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

6)☐ Claim(s) _____ is/are allowed.

7)☑ Claim(s) 1-10 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 _____ 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 7/7/17 .

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

4) ☐ Other: _____ .

DETAILED CORRESPONDENCE

Previous Rejections

Applicant's arguments, filed 7/7/17, have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 103

The following is a quotation of pre-AIA 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, 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.

Claim 1 is rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Rahman et al (WO 2003/030864), in view of Vucenik et al (J Nutr, 133, 2003, 3778S-3784S) as evidenced by of Nicolau et al (WO 2003/092700).

Rahman disclosed liposomal formulations of entrapped irinotecan, at the abstract and title. The liposomes comprised phospholipids, e.g., phosphatidylcholine, at claims 11 and 17. The compositions were useful in the treatment of cancer, at the abstract.

The compositions comprised 1-50 wt. % irinotecan and 1-95 wt. % phosphatidylcholine, at page 5 and lines 4-11. At 50 wt. % irinotecan (e.g., 0.5 ÷ 587 g/mol = 0.00085 mol) and 95 wt. % phosphatidylcholine (e.g., 0.95 ÷ 758 g/mol = 0.00125 mol),

Rahman's molar ratio of irinotecan to phospholipid is 0.7:1 (e.g. 0.00085 ÷ 0.00125), which falls within the instantly recited range of 0.15:1 to 1.5:1.

Rahman did not disclose pyrophosphate, as recited in claim 1.

Vucenik disclosed that inositol hexaphosphate (IP6) has a striking anticancer effect. Further, in addition to reducing cell proliferation, IP6 increases differentiation of malignant cells, often resulting in a reversion to the normal phenotype. Enhanced immunity and antioxidant properties of the drug further contribute to tumor cell destruction (abstract).

Vucenik did not disclose irinotecan.

Nicolau evidenced that inositol hexaphosphates are inositol pyrophosphates, which are compounds comprising internal pyrophosphates (Nicolau, at the title and abstract).

Since Rahman disclosed the treatment of cancer with anticancer agents generally (abstract), it would have been prima facie obvious to one of ordinary skill in the art to have incorporated inositol hexaphosphate within Rahman, as taught by Vucenik. An ordinarily skilled artisan would have been motivated because inositol hexaphosphate demonstrates a striking anticancer effect by reducing cell proliferation and increasing differentiation of malignant cells, which often results in a reversion to the normal phenotype. Additionally, enhanced immunity and antioxidant properties of the drug further contribute to tumor cell destruction, as taught by Vucenik at the abstract.

The MPEP, at section 2144.07, states that generally, it is prima facie obvious to select a known material for incorporation into a composition, based on its recognized suitability for its intended use. In the instant case, it is prima facie obvious to select inositol

hexaphosphate for incorporation into a composition, based on its recognized suitability for its intended use as an anticancer agent, as taught by Vucenik.

The instant claim 1 recites a 0.15:1 to 1.5:1 molar ratio of irinotecan to phospholipid. Rahman disclosed a 0.7:1 irinotecan to phospholipid molar ratio, as discussed above. In the case where the claimed ranges "overlap or lie inside ranges disclosed by the prior art", a prima facie case of obviousness exists. MPEP 2144.05 A.

Claim 1 recites compositions comprising pyrophosphates. Vucenik disclosed compositions comprising inositol hexaphosphate. Nicolau evidenced that inositol hexaphosphate contains an internal pyrophosphate. Therefore, it appears that the compositions of the instant claims and those of the prior art would reasonably be expected to have substantially the same physical and chemical properties. This is because the claims recite a pyrophosphate, and Vucenik teaches inositol hexaphosphate, which has an internal pyrophosphate, as evidenced by Nicolau.

Applicant's Arguments and Examiner's Response

Applicants argued that the Office Action failed to make a prima facie case of obviousness.

The Examiner disagrees that the Office Action failed to make a prima facie case of obviousness. Rahman disclosed liposomal formulations of entrapped irinotecan for the treatment of cancer, however, Rahman did not disclose pyrophosphate. But, Vucenik

disclosed that inositol hexaphosphate (IP6) has a striking anticancer effect. And, Nicolau evidenced that inositol hexaphosphate comprises an internal pyrophosphate ring.

Since Rahman disclosed the treatment of cancer with anticancer agents generally (abstract), it would have been prima facie obvious to one of ordinary skill in the art to have incorporated inositol hexaphosphate within Rahman, as taught by Vucenik. An ordinarily skilled artisan would have been motivated because inositol hexaphosphate demonstrates a striking anticancer effect by reducing cell proliferation and increasing differentiation of malignant cells, which often results in a reversion to the normal phenotype. Additionally, enhanced immunity and antioxidant properties of the drug further contribute to tumor cell destruction, as taught by Vucenik at the abstract.

The MPEP, at section 2144.07, states that generally, it is prima facie obvious to select a known material for incorporation into a composition, based on its recognized suitability for its intended use. In the instant case, it is prima facie obvious to select inositol hexaphosphate for incorporation into a composition, based on its recognized suitability for its intended use as an anticancer agent, as taught by Vucenik.

Applicants argued that Nicolau does not disclose that inositol hexaphosphates are inositol pyrophosphates. Applicants argued that Nicolau disclosed (abstract) modified inositol hexaphosphate comprising an internal pyrophosphate ring. Applicants argued that an ordinarily skilled artisan would recognize that inositol hexaphosphate and modified versions thereof containing pyrophosphate rings are not the same chemical entities. Applicants argued that Nicolau teaches that specific chemical reactions must be

performed to convert inositol hexaphosphate to inositol hexaphosphate derivatives containing pyrophosphate rings.

The Examiner disagrees with the Applicants. Nicolau evidenced that inositol hexaphosphate has an internal pyrophosphate ring. As such, inositol hexaphosphate comprises pyrophosphate. In the broadest reasonable interpretation of claim 1, the combination of Rahman and Vucenik read on claim 1, as evidenced by Nicolau. This is because pyrophosphates can be various compounds. For example, pyrophosphates can be salts (e.g., sodium pyrophosphate), or a part of a molecule (e.g., a high energy biochemical bond). So, the claims are not limited to a specific compound, and thus, include Vucenik's inositol hexaphosphate, which comprises an internal pyrophosphate ring, as evidenced at the abstract of Nicolau, which states a "modified inositol hexaphosphate comprising an internal pyrophosphate ring."

Applicants argued that Nicolau does not disclose that inositol hexaphosphates have internal pyrophosphates; that Nicolau disclosed transformations to modify the inositol hexaphosphates to compounds having the internal pyrophosphate ring.

The Examiner acknowledges that Nicolau's compounds are modified derivatives of inositol hexaphosphates. The modification was to increase the delivery of the compound across the erythrocyte membrane, in order to increase the binding affinity with hemoglobin (see Nicolau, page 8, lines 3-8). Inositol hexaphosphates have a pyrophosphate moiety. As evidence rebutting applicant's arguments only, and not as a basis for rejection, the Examiner cites Onnebo et al (Cell, 129, May 18, 2007).

Onnebo disclosed that inositol phosphate rings comprise pyrophosphate moieties. At the first paragraph, Onnebo disclosed inositol phosphates, including species with up

to eight phosphates, and stated that "although the mechanisms of action of inositol pyrophosphates in cellular processes remain unclear, IP_7 (for example) has been shown to directly transfer the energetic β phosphate of the pyrophosphate moiety to multiple proteins..." As such, it appears that inositol hexaphosphates comprise pyrophosphate moieties, as evidenced by Onnebo.

Applicants argued that the present claims do not mention inositol hexaphosphate or any other inositol-based chemical structure, such as an inositol hexaphosphate containing an internal pyrophosphate ring. Applicants argued that the structures of pyrophosphate and inositol are different. Applicants argued that Rahman does not disclose pyrophosphate, and that Nicolau and Vucenik do not cure the deficiencies of Rahman.

The Examiner responds that the prior art disclosed compounds (e.g., inositol hexaphosphate) that inherently possess pyrophosphate, as evidenced by Nicolau and Onnebo (e.g., discussed above).

Applicants argued that claims 2-10 are patentable, based on dependency from claim 1.

The Examiner disagrees that claims 2-10 are patentable. The Examiner responds that patentable subject matter has not been identified in claim 1.

Claims 2-3 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Rahman et al (WO 2003/030864), in view of Vucenik et al (J Nutr, 133, 2003, 3778S-3784S) and further in view of Mentrup Edgar et al (USP 5,498,420), as evidenced by of Nicolau et al (WO 2003/092700).

The 35 U.S.C. 103(a) rejection over Rahman, in view of Vucenik and as evidenced by Nicolau, has been discussed above. Additionally, Rahman disclosed, at claims 11 and 17, that the liposome forming material was phosphatidyl choline and cholesterol.

Although Rahman disclosed phosphatidyl choline as a lipid forming material, Rahman did not specifically disclose lecithin, as recited in claims 2-3.

However, Mentrup Edgar disclosed liposome vesicles comprised of phosphatidyl choline, wherein the phosphatidyl choline was in the form of a natural lecithin, at claims 1 and 5.

Mentrup Edgar did not disclose irinotecan.

Since Rahman disclosed liposomes comprised of phosphatidyl choline, it would have been prima facie obvious to one of ordinary skill in the art to have included lecithin within Rahman's composition, as taught by Mentrup Edgar. It is prima facie obvious to select lecithin for incorporation into a liposome, based on its recognized suitability for its intended use as a vesicle forming lipid, as taught by Mentrup Edgar at claims 1 and 5.

Claim 3 is rendered prima facie obvious because Rahman disclosed 1-95 wt. % of the liposome forming material (e.g., phosphatidyl choline and cholesterol), as discussed above.

At 95 wt. % phosphatidylcholine (e.g., lecithin) (e.g., 0.95 ÷ 758 g/mol = 0.00125 mol) and 30 wt. % cholesterol (e.g., 0.30 ÷ 387 g/mol = 0.0008 mol), Rahman's molar ratio of phosphatidyl choline (e.g., lecithin) to cholesterol is the instantly recited 3:2 (e.g. 0.00125 + 0.0008).

Applicant's Arguments and Examiner's Response

The arguments over claims 2-3 were presented above.

Claims 4-9 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Rahman et al (WO 2003/030864), in view of Vucenik et al (J Nutr, 133, 2003, 3778S-3784S) and further in view of Ellens et al (US 2004/0013720) as evidenced by of Nicolau et al (WO 2003/092700).

The 35 U.S.C. 103(a) rejection over Rahman, in view of Vucenik has been discussed above.

Additionally, Rahman disclosed phospholipids as liposome-forming lipids, in general, at page 8 and lines 7-8.

However, Rahman did not specifically disclose DSPC, as recited in claims 4-5 and 8-9. Also, Rahman did not disclose an amphipathic polymer comprising a polyethylene glycol-lipid, as recited in claims 5-9.

Ellens disclosed liposomes as drug delivery vesicles, at the abstract. The liposomes comprised phospholipids, as vesicle forming lipids commonly known in the art; DSPC was specifically disclosed as said phospholipid, at [0023-0025].

Polyethylene glycols (PEG) (e.g., hydrophilic polymer) were disclosed to increase blood circulation times, and to provide improved delivery of the liposomes, at [0014 and 0038]. The polyethylene glycols were disclosed as methoxy-capped (e.g., mPEG), and as having a molecular weight of about 300-7,000, at [0040]. Finally, the PEG was disclosed as PEG-DSPE (e.g., mPEG-DSPE), at 0-20 mole percent, at [0082].

Ellens did not disclose pyrophosphate.

Since Rahman disclosed liposomes generally comprised of phospholipids as vesicle forming lipids, it would have been prima facie obvious to one of ordinary skill in the art to have included DSPC within Rahman, as taught by Ellens. An ordinarily skilled artisan would have been motivated because DSPC is commonly known in the art as a liposome vesicle forming lipid, as taught by Ellens at [0023-0025]. Further, It is prima facie obvious to select DSPC for incorporation into a liposome, based on its recognized suitability for its intended use as a vesicle forming lipid, as taught by Ellens.

Since Rahman disclosed liposomes, it would have been prima facie obvious to one of ordinary skill in the art to have incorporated an amphipathic polymer comprising a polyethylene glycol (e.g., mPEG-DSPE) within Rahman, as taught by Ellens. An ordinarily skilled artisan would have been motivated because said polymers provide improved delivery of the liposomes, as taught by Ellens at [0014 and 0038].

Claim 4 recites DSPC and cholesterol in a 3:2 mole ratio. Rahman disclosed 1-95 wt. % of the liposome forming material (e.g., phospholipids and cholesterol), as discussed above. Ellens disclosed DSPC as a commonly known phospholipid, as discussed above.

At 95 wt. % DSPC (e.g., 0.95 ÷ 790 g/mol = 0.0012 mol) and 30 wt. % cholesterol (e.g., 0.30÷387 g/mol = 0.0008 mol), Rahman's molar ratio of phospholipid (e.g., DSPC) to cholesterol is the instantly recited 3:2 (e.g. 0.0012 ÷ 0.0008).

Claims 5-7 are rendered prima facie obvious because Ellens disclosed mPEG-DSPE having a molecular weight of 300-7,000, as discussed above.

Claim 7 recites a PEG-DSPE molecular weight of from about 250 to about 20,000. Ellens disclosed mPEG-DSPE with a molecular weight of 300-7,000. A prima facie case of obviousness exists because of overlap, as discussed above.

Claims 8-9 are rendered prima facie obvious because Rahman disclosed a 3:2 molar ratio of phospholipid to cholesterol, as discussed above. Ellens disclosed DSPC, as discussed above. Further, Ellens disclosed PEG-DSPE (e.g., mPEG-DSPE), at 0-20 mole percent, as discussed above.

Claims 8-9 recite mPEG-DSPE at 0.015 mole. Further, claim 9 recites a molecular weight of PEG of 2,000. Ellens disclosed mPEG-DSPE at 0-20 mole. Additionally, Ellens disclosed PEG having a molecular weight of 300-7,000 as discussed above. A prima facie case of obviousness exists because of overlap, as discussed above.

Applicant's Arguments and Examiner's Response

The arguments over claims 4-9 were presented above.

Claim 10 is rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Rahman et al (WO 2003/030864), in view of Vucenik et al (J Nutr, 133, 2003, 3778S-3784S) and further in view of Abai et al (WO 1990/014074) as evidenced by of Nicolau et al (WO 2003/092700).

The 35 U.S.C. 103(a) rejection over Rahman, in view of Vucenik has been discussed above.

Rahman disclosed 1-50 wt. % of irinotecan, as discussed above. At 1 wt. % irinotecan, the composition contained 5.87 g irinotecan (e.g., 0.01 * 587 g/mol = 5.87

g); at 50 wt. % irinotecan, the composition contained 293 g irinotecan (e.g., 0.5 * 587 g/mol = 293 g). As such, Rahman disclosed compositions containing from 5.87 to 293 g of irinotecan.

Additionally, Rahman disclosed that the liposomes can be formed of negatively charged lipids, at page 4 and line 34.

However, Rahman did not specifically disclose the molar amount of phospholipids, as recited in claims 11 and 17.

Abai disclosed liposomal formulations comprised of at least 1 mole percent of negatively charged phospholipids, at claim 1.

Abai did not disclose pyrophosphate.

Since Rahman disclosed liposomes comprised of negative phospholipids, it would have been prima facie obvious to one of ordinary skill in the art to have included said phospholipids within Rahman at the amount of 1 mole, as taught by Abai. An ordinarily skilled artisan would have been motivated to have included the phospholipid in an amount sufficient to form the liposome, as taught by Abai at claim 1.

An ordinarily skilled artisan would have been motivated to have included negatively charged phospholipids within Rahman at 1 mole, because at said amount, the ingredients are vesicle forming lipids, as taught by Abai.

The combination of Rahman and Abai disclosed 5.87-293 g irinotecan (e.g., as discussed above by Rahman) per 1 mole phospholipid.

The instant claim 10 recites 136.2 g irinotecan per 1 mole of phospholipid. Rahman disclosed 5.87-293 g irinotecan. Abai disclosed 1 mole of phospholipid. A prima facie case of obviousness exists because of overlap, as discussed above.

Applicant's Arguments and Examiner's Response

The arguments over claim 10 was presented above.

Nonstatutory Double Patenting

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 1-10 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1, 3-4, 8 and 10-11 of copending Application No. 14/964,239.

Although the claims at issue are not identical, they are not patentably distinct from each other because the species recited in the copending claims (e.g. liposome comprising irinotecan and a polyphosphorylated polyol) falls within the genus (e.g., irinotecan liposome composition) recited in the claims of the instant application, and thus read on the instant claims.

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

Claims 1-10 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-3, 5-11 and 17-20 of copending Application

No. 14/966,458, in view of Vucenik et al (J Nutr, 133, 2003, 3778S-3784S) as evidenced by of Nicolau et al (WO 2003/092700).

Although the claims at issue are not identical, they are not patentably distinct from each other. The copending claims recite all of the features instantly recited for the liposome except for pyrophosphate. The instant claims require pyrophosphate, and such an ingredient is not recited by the copending claims.

Vucenik disclosed inositol hexaphosphate as an anticancer agent. Nicolau evidenced that inositol hexaphosphates are inositol pyrophosphates, which are compounds comprising internal pyrophosphates (Nicolau, at the title and abstract).

It would have been prima facie obvious to one of ordinary skill in the art to have included inositol hexaphosphate in the copending formulation, because inositol hexaphosphate is an anticancer agent, as discussed above, and as taught by Vucenik.

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

Claims 1-10 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-24 of copending Application No. 15/364,021, in view of Vucenik et al (J Nutr, 133, 2003, 3778S-3784S) as evidenced by of Nicolau et al (WO 2003/092700).

Although the claims at issue are not identical, they are not patentably distinct from each other. The copending claims recite all of the features instantly recited for the liposome except for pyrophosphate. The instant claims require pyrophosphate, and such an ingredient is not recited by the copending claims.

Vucenik disclosed inositol hexaphosphate as an anticancer agent. Nicolau evidenced that inositol hexaphosphates are inositol pyrophosphates, which are compounds comprising internal pyrophosphates (Nicolau, at the title and abstract).

It would have been prima facie obvious to one of ordinary skill in the art to have included inositol hexaphosphate in the copending formulation, because inositol hexaphosphate is an anticancer agent, as discussed above, and as taught by Vucenik.

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

Claims 1-10 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-10 of copending Application No. 15/363,761, in view of Vucenik et al (J Nutr, 133, 2003, 3778S-3784S) as evidenced by of Nicolau et al (WO 2003/092700).

Although the claims at issue are not identical, they are not patentably distinct from each other. The copending claims recite all of the features instantly recited for the liposome except for pyrophosphate. The instant claims require pyrophosphate, and such an ingredient is not recited by the copending claims. Vucenik disclosed inositol hexaphosphate as an anticancer agent. Nicolau evidenced that inositol hexaphosphates are inositol pyrophosphates, which are compounds comprising internal pyrophosphates (Nicolau, at the title and abstract).

It would have been prima facie obvious to one of ordinary skill in the art to have included inositol hexaphosphate in the copending formulation, because inositol hexaphosphate is an anticancer agent, as discussed above, and as taught by Vucenik.

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

Applicant's Arguments and Examiner's Response

Applicants requested that the nonobviousness type double patenting rejections be held in abeyance until all other rejections in the application have been overcome.

The Examiner responds that the rejections are maintained because all other rejections in the application have not been overcome.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CELESTE A RONEY whose telephone number is (571)272-5192. The examiner can normally be reached on M-Th: 7a-5p.

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, Frederick Krass can be reached on 571-272-0580. 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.

/CELESTE A RONEY/
Examiner, Art Unit 1612

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/363,978	11/29/2016	Keelung Hong	263266-411574	5428

139696 7590 12/14/2017

Honigman Miller Schwartz and Cohn LLP/Ipsen
350 East Michigan Avenue, Suite 300
Kalamazoo, MI 49007

EXAMINER	
RONEY, CELESTE A	

ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
12/14/2017	ELECTRONIC

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

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

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

patents@honigman.com
lzerby@honigman.com
arhoades@honigman.com

Applicant-Initiated Interview Summary	Application No. 15/363,978	Applicant(s) Hong et al.	
	Examiner CELESTE A RONEY	Art Unit 1612	AIA Status No

All participants (applicant, applicants representative, PTO personnel):

(1) CELESTE A. RONEY.

(2) Christopher Forbes and Cindy Bott.

(3) Eileen Ennis.

(4) Fred Krass.

Date of Interview: 07 December 2017.

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

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

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

Claim(s) discussed: 1.

Identification of prior art discussed: Of Record.

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

Applicants argued that the irinotecan pyrophosphate of the instant invention is a salt, and as such, overcomes the prior art. Applicants discussed potential claim amendments to clarify that the composition is a salt. Applicants and Examiner discussed the AFCP 2.0 program as a potential path forward with claim amendments. Claim amendments will be considered upon receipt..

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

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

☐ Attachment

/CELESTE A RONEY/ Primary Examiner, Art Unit 1612	

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) 1.133 Interviews
Paragraph (b)

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

37 CFR §1.2 Business to be transacted in writing.
All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

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

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiners responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicants correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

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

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

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

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

Examiner to Check for Accuracy

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

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/364,021	11/29/2016	Keelung Hong	239669-405560/1001130US21	8037

133156 7590 03/09/2017

Honigman Miller Schwartz and Cohn LLP
350 East Michigan Avenue
Suite 300
Kalamazoo, MI 49007

EXAMINER
LIU, TRACY

ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
03/09/2017	ELECTRONIC

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

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

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

patents@honigman.com
lbroecker@honigman.com
lzerby@honigman.com

Office Action Summary	Application No. 15/364,021	Applicant(s) HONG ET AL.	
	Examiner TRACY LIU	Art Unit 1612	AIA (First Inventor to File) Status No

-- 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 *11/29/2016*.

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

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

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; 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) *1-24* is/are pending in the application.

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

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-24* 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 *11/29/2016* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

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

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

Priority under 35 U.S.C. § 119

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

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

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

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

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

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

Attachment(s)

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

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

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

4) ☐ Other: _____.

DETAILED ACTION

The present application is being examined under the pre-AIA first to invent provisions. Claims included in the prosecution are claims 1-24.

Claim Rejections - 35 USC § 103

The following is a quotation of pre-AIA 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, 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.

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 pre-AIA 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.

1. Claims 1, 2, 10 and 11 is/are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Rahman et al. (WO 03/030864, Apr. 17, 2003) in view of Schroeder et al. (DE 4,320,597, Jan. 5, 1995), Weiner et al. (US 4,397,846, Aug. 9, 1983) and Bolotin et al. (US 2004/0156891, Aug. 12, 2004).

Rahman et al. disclose a therapeutic composition comprising liposome entrapped irinotecan (abstract). Any suitable liposome-forming material can be used in the liposome. Suitable liposome-forming compounds include phospholipid, phosphatidyl choline (i.e. lecithin) and cholesterol (page 4, lines 7-9). The liposome, once formed, can be filtered through suitable filters to control their size distribution. The liposome can be filtered through a 100 nm filter to obtain a liposome having a diameter of about 100 nm or less (page 3, lines 22-28). Other therapeutic agents can be used in combination with irinotecan (page 7, lines 4-5). The composition is used to treat cancer (abstract).

Rahman et al. differ from the instant claims insofar as not disclosing wherein the liposome comprises a polyphosphate having 13-18 phosphate units per polyphosphate molecule.

However, Schroeder et al. disclose the use of polyphosphates having a chain length of greater than three phosphate units as a medicament (claim 1). Polyphosphates with a chain length of more than 3 phosphate units are useful as antiviral agents with immunomodulating activity, specifically for the treatment of AIDS and ARC (abstract).

Weiner et al. disclose lipid vesicles containing a biologically active agent (col. 2, lines 39-40). Lipid vesicles are also known as liposomes (col. 1, line 9). The biologically active agent includes inositol hexaphosphate (claim 11). Inositol hexaphosphate is a polyphosphate (col. 4, lines 10-11).

It would have been *prima facie* obvious to one of ordinary skill in the art to have incorporated polyphosphates having a chain length of greater than three phosphate

units into the liposome of Rahman et al. since the liposome may comprise other therapeutic agents and polyphosphates with a chain length of more than 3 phosphate units are suitable therapeutic agents that are useful as antiviral agents with immunomodulating activity, specifically for the treatment of AIDS and ARC as taught by Schroeder et al. It would have been obvious to one of ordinary skill in the art that polyphosphates with a chain length of more than 3 phosphate units may be incorporated into liposomes since liposomes comprising polyphosphate as active agents are known as taught by Weiner et al.

The combined teachings of Rahman et al., Schroeder et al., and Weiner et al. do not disclose wherein the composition has a mole ratio of irinotecan to lipid between 0.15:1 to 1.5:1.

However, Bolotin et al. disclose a liposomal composition comprising an analgesic drug (claim 1). The molar ratio of encapsulated analgesic drug to lipid in said liposomal analgesic composition is at least 1.0 (claim 6).

It would have been prima facie obvious to one of ordinary skill in the art to have the mole ratio of irinotecan to lipid to be at least 1.0 since at least 1.0 is an effective drug:lipid mole ratio for liposomes comprising drugs as taught by Bolotin et al.

In regards to instant claim 10 reciting wherein the liposomes have a mean size of 112±15.5 nm and 112.3±15.5 nm, respectively, measured by QELS, Rahman et al. disclose wherein irinotecan liposomes have a size of 100 nm. Thus, it would have been obvious to one of ordinary skill in the art to have formulated a liposome of such size when measured with a variety of liposomal measuring techniques, such as QELS.

2. Claims 3, 4 and 13 is/are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Rahman et al. (WO 03/030864, Apr. 17, 2003) in view of Schroeder et al. (DE 4,320,597, Jan. 5, 1995), Weiner et al. (US 4,397,846, Aug. 9, 1983), Bolotin et al. (US 2004/0156891, Aug. 12, 2004) and further in view of Gupta et al. (WO 2000/009071, Feb. 24, 2000).

The teachings of Rahman et al., Schroeder et al, Weiner et al. and Bolotin et al. are discussed above. Rahman et al., Schroeder et al, Weiner et al. and Bolotin et al. do not disclose wherein the lecithin and cholesterol are in a 3:2 mole ratio and wherein the liposome comprises DSPC, wherein DSPC and cholesterol are in a 3:2 mole ratio.

However, Gupta et al. disclose a liposomal formulation useful in treatment of cancer and other proliferative diseases. The formulation comprises phospholipids and/or sterols both in molar ratio of 1-15 (claim 1). Suitable phospholipids include distearoyl phosphatidyl choline (page 5, line 23).

It would have been *prima facie* obvious to one of ordinary skill in the art to have incorporated distearoyl phosphatidyl choline (DSPC) into the liposome of Rahman et al. since distearoyl phosphatidyl choline is a known liposome-forming compound as taught by Gupta et al.

It would have been *prima facie* obvious to one of ordinary skill in the art to have lecithin:cholesterol or distearoyl phosphatidyl choline:cholesterol in a molar ratio ranging from 1-15 since is an effective molar ratio of phospholipids and sterols to formulate a liposome for treating cancer as taught by Gupta et al.

3. Claims 5-7, 12, 14 and 15 is/are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Rahman et al. (WO 03/030864, Apr. 17, 2003) in view of Schroeder et al. (DE 4,320,597, Jan. 5, 1995), Weiner et al. (US 4,397,846, Aug. 9, 1983), Bolotin et al. (US 2004/0156891, Aug. 12, 2004), Gupta et al. (WO 2000/009071, Feb. 24, 2000) and further in view of Woodle et al. (US 5,013,556, May 7, 1991).

The teachings of Rahman et al., Schroeder et al, Weiner et al. and Bolotin et al. are discussed above. Rahman et al., Schroeder et al, Weiner et al. and Bolotin et al. do not disclose wherein the liposome comprises an amphipathic polymer comprising a polyethylene glycol-lipid and wherein the grams of irinotecan to moles of phospholipid is in the ratio of 0.15:1 to 0.55:1.

However, Woodle et al. disclose a liposome composition which contains an amphipathic lipid derivatized with a polyalkylether, as exemplified by phosphatidylethanolamine derivatized with polyethylene glycol. The derivatized lipid enhances the circulation time of the liposome several folds (abstract). The polyethylene glycol has a molecular weight between about 1,000 to 5,000 daltons (claim 21). The liposome contain 10-40 mole percent cholesterol, 40-85 mole percent neutral phospholipid and 5-15 mole percent phospholipid derivatized with polyethylene glycol (claim 9).

It would have been *prima facie* obvious to one of ordinary skill in the art to have incorporated phosphatidylethanolamine derivatized with polyethylene glycol into the liposome of Rahman et al. since phosphatidylethanolamine derivatized with

polyethylene glycol enhances the circulation time of liposomes as taught by Woodle et al.

It would have been *prima facie* obvious to one of ordinary skill in the art for the grams of irinotecan to moles of phospholipid be in the ratio of 0.5:1 since Rahman et al. disclose wherein the liposome comprises 0.1 to 50 weight percent irinotecan and Woodle et al. disclose wherein liposomes may comprise 50 mole percent phospholipid. Thus, assuming a 100 g liposome, the liposome may comprise 25 g irinotecan and 50 mole percent phospholipid, thus having a 0.5:1 ratio of grams of irinotecan to moles of phospholipid.

4. Claim 8 is/are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Rahman et al. (WO 03/030864, Apr. 17, 2003) in view of Schroeder et al. (DE 4,320,597, Jan. 5, 1995), Weiner et al. (US 4,397,846, Aug. 9, 1983), Bolotin et al. (US 2004/0156891, Aug. 12, 2004), Gupta et al. (WO 2000/009071, Feb. 24, 2000) and further in view of Cullis et al. (US 6,417,326, Jul. 9 , 2002).

The teachings of Rahman et al., Schroeder et al, Weiner et al. and Bolotin et al. are discussed above. Rahman et al., Schroeder et al, Weiner et al. and Bolotin et al. do not disclose the liposome comprises N-(methoxy-poly(ethylene glycol)-oxycarbonyl)-distearoylphosphatidylethanolamine (PEG-DSPE).

However, Cullis et al. disclose liposomes comprising DSPE-PEG_{2000} (Fig. 8).

It would have been *prima facie* obvious to one of ordinary skill in the art to have incorporated DSPE-PEG_{2000} into the liposome of Rahman et al. since DSPE-PEG_{2000} is a known liposome-forming compound as taught by Cullis et al.

In regards to instant claim 8 reciting wherein the mole ratio of DSPC, cholesterol, and PEG-DSPE is 3:2:0.015, Gupta et al. disclose wherein the mole ratio of phospholipids and sterols in liposomes is from 1-15.

5. Claims 9 and 16 is/are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Rahman et al. (WO 03/030864, Apr. 17, 2003) in view of Schroeder et al. (DE 4,320,597, Jan. 5, 1995), Weiner et al. (US 4,397,846, Aug. 9, 1983), Bolotin et al. (US 2004/0156891, Aug. 12, 2004), Gupta et al. (WO 2000/009071, Feb. 24, 2000) and further in view of Hardee et al. (US 6,083,923, Jul. 4, 2000).

The teachings of Rahman et al., Schroeder et al, Weiner et al., Bolotin et al. and Gupta et al. are discussed above. Rahman et al., Schroeder et al, Weiner et al., Bolotin et al. and Gupta et al. do not disclose the liposome comprises MPEG-2000-DSPE.

However, Hardee et al. disclose liposomes comprising DSPE-$MPEG_{2000}$ (col. 28, lines 2-3).

It would have been *prima facie* obvious to one of ordinary skill in the art to have incorporated DSPE-$MPEG_{2000}$ into the liposome of Rahman et al. since DSPE-$MPEG_{2000}$ is a known liposome-forming compound as taught by Hardee et al.

In regards to instant claims 9 and 16 reciting wherein the mole ratio of DSPC, cholesterol, and MPEG-2000-DSPE is 3:2:0.015, Gupta et al. disclose wherein the mole ratio of phospholipids and sterols in liposomes is from 1-15.

6. Claims 17-21 is/are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Rahman et al. (WO 03/030864, Apr. 17, 2003) in view of Schroeder et al. (DE 4,320,597, Jan. 5, 1995), Weiner et al. (US 4,397,846, Aug. 9, 1983), Bolotin et al. (US 2004/0156891, Aug. 12, 2004) and further in view of Steffen et al. (US 4,649,155, Mar. 10, 1987).

The teachings of Rahman et al., Schroeder et al, Weiner et al. and Bolotin et al. are discussed above. Rahman et al., Schroeder et al, Weiner et al. and Bolotin et al. do not disclose wherein the ratio of irinotecan to phospholipid is 200 g per mol phospholipid, 300 g per mol phospholipid, 400 g per mol phospholipid, 500 g per mol phospholipid or 550 g per mol phospholipid.

However, Steffen et al. disclose an injectable aqueous micellar solution comprising vitamin E, a phospholipid and a cholanic acid or salt thereof. The solution contains at least about 100 g of vitamin E per mol of phospholipid (claim 1).

It would have been *prima facie* obvious to one of ordinary skill in the art to have the ratio of irinotecan to phospholipid be at least about 100 g per mol of phospholipid since this is an effective amount of active agent to phospholipid ratio as taught by Steffen et al.

7. Claim 22 is/are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Rahman et al. (WO 03/030864, Apr. 17, 2003) in view of Schroeder et al. (DE 4,320,597, Jan. 5, 1995), Weiner et al. (US 4,397,846, Aug. 9, 1983), Hardee et al. (US 6,083,923, Jul. 4, 2000) and Steffen et al. (US 4,649,155, Mar. 10, 1987).

Rahman et al. disclose a therapeutic composition comprising liposome entrapped irinotecan (abstract). Any suitable liposome-forming material can be used in the liposome. Suitable liposome-forming compounds include phospholipid, phosphatidyl choline (i.e. lecithin) and cholesterol (page 4, lines 7-9). The liposome, once formed, can be filtered through suitable filters to control their size distribution. The liposome can be filtered through a 100 nm filter to obtain a liposome having a diameter of about 100 nm or less (page 3, lines 22-28). Other therapeutic agents can be used in combination with irinotecan (page 7, lines 4-5). The composition is used to treat cancer (abstract).

Rahman et al. differ from the instant claims insofar as not disclosing wherein the liposome encapsulates a polyphosphate.

However, Schroeder et al. disclose the use of polyphosphates having a chain length of greater than three phosphate units as a medicament (claim 1). Polyphosphates with a chain length of more than 3 phosphate units are useful as antiviral agents with immunomodulating activity, specifically for the treatment of AIDS and ARC (abstract).

Weiner et al. disclose lipid vesicles containing a biologically active agent (col. 2, lines 39-40). Lipid vesicles are also known as liposomes (col. 1, line 9). The biologically

active agent includes inositol hexaphosphate (claim 11). Inositol hexaphosphate is a polyphosphate (col. 4, lines 10-11).

It would have been *prima facie* obvious to one of ordinary skill in the art to have incorporated polyphosphates having a chain length of greater than three phosphate units into the liposome of Rahman et al. since the liposome may comprise other therapeutic agents and polyphosphates with a chain length of more than 3 phosphate units are suitable therapeutic agents that are useful as antiviral agents with immunomodulating activity, specifically for the treatment of AIDS and ARC as taught by Schroeder et al. It would have been obvious to one of ordinary skill in the art that polyphosphates with a chain length of more than 3 phosphate units may be incorporated into liposomes since liposomes comprising polyphosphate as active agents are known as taught by Weiner et al.

The combined teachings of Rahman et al., Schroeder et al., and Weiner et al. do not disclose wherein the liposome comprises a PEGylated lipid.

However, Hardee et al. disclose liposomes comprising DSPE-$MPEG_{2000}$ (col. 28, lines 2-3).

It would have been *prima facie* obvious to one of ordinary skill in the art to have incorporated DSPE-$MPEG_{2000}$ into the liposome of Rahman et al. since DSPE-$MPEG_{2000}$ is a known liposome-forming compound as taught by Hardee et al.

The combined teachings of Rahman et al., Schroeder et al., Weiner et al. and Hardee et al. do not disclose wherein the composition has a 465.6±26.5 mg irinotecan per mmol phospholipid.

However, Steffen et al. disclose an injectable aqueous micellar solution comprising vitamin E, a phospholipid and a cholanic acid or salt thereof. The solution contains at least about 100 g of vitamin E per mol of phospholipid (claim 1).

It would have been *prima facie* obvious to one of ordinary skill in the art to have at least about 100 g irinotecan per mol of phospholipid since this is an effective amount of active agent to phospholipid ratio as taught by Steffen et al.

In regards to instant claim 22 reciting wherein the liposomes have a mean size of 112.3±15.5 nm, respectively, measured by QELS, Rahman et al. disclose wherein irinotecan liposomes have a size of 100 nm. Thus, it would have been obvious to one of ordinary skill in the art to have formulated a liposome of such size when measured with a variety of liposomal measuring techniques, such as QELS.

8. Claims 23 and 24 is/are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Rahman et al. (WO 03/030864, Apr. 17, 2003) in view of Schroeder et al. (DE 4,320,597, Jan. 5, 1995), Weiner et al. (US 4,397,846, Aug. 9, 1983), Hardee et al. (US 6,083,923, Jul. 4, 2000), Steffen et al. (US 4,649,155, Mar. 10, 1987) and further in view of Gupta et al. (WO 2000/009071, Feb. 24, 2000).

The teachings of Rahman et al., Schroeder et al.,Weiner et al., Hardee et al., and Steffen et al. are discussed above. Rahman et al., Schroeder et al.,Weiner et al., Hardee et al., and Steffen et al. do not disclose wherein the liposome comprises DSPC and wherein the DSPC and cholesterol are in a mole ratio of 3:2 and the DSPC, cholesterol and MPEG-2000-DSPE is in a mole ratio of 3:2:0.015.

However, Gupta et al. disclose a liposomal formulation useful in treatment of cancer and other proliferative diseases. The formulation comprises phospholipids and/or sterols both in molar ratio of 1-15 (claim 1). Suitable phospholipids include distearoyl phosphatidyl choline (page 5, line 23).

It would have been *prima facie* obvious to one of ordinary skill in the art to have incorporated distearoyl phosphatidyl choline (DSPC) into the liposome of Rahman et al. since distearoyl phosphatidyl choline is a known liposome-forming compound as taught by Gupta et al.

It would have been *prima facie* obvious to one of ordinary skill in the art to have distearoyl phosphatidyl choline:cholesterol or DSPC:cholesterol:MPEG-2000-DSPE in a molar ratio ranging from 1-15 since is an effective molar ratio of phospholipids and sterols to formulate a liposome for treating cancer as taught by Gupta et al.

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 1-24 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-10 of copending Application No. **15/363,978**, claims 1-10 of copending Application No. **15/363,761**, claims 1-19 of copending Application No. **15/363,923** in view of Rahman et al. (WO 03/030864, Apr. 17, 2003), Schroeder et al. (DE 4,320,597, Jan. 5, 1995) and Weiner et al. (US 4,397,846, Aug. 9, 1983). The pending claims differ from the copending claims insofar as reciting therein the liposome have a mean size of 112.3±15.5 nm measured by QELS. However, Rahman et al. disclose wherein irinotecan liposomes have a size of 100 nm. Thus, it would have been obvious to one of ordinary skill in the art to have formulated a liposome of such size when measured with a variety of liposomal measuring techniques, such as QELS, since 100 nm is an effective size for irinotecan liposomes. Furthermore, the pending claims differ from the copending claims insofar as reciting a polyphosphate having 13-18 phosphate units per polyphosphate molecule. However, Schroeder et al. disclose the use of polyphosphates having a chain length of greater than three phosphate units as a medicament (claim 1). Polyphosphates with a chain length of more than 3 phosphate units are useful as antiviral agents with immunomodulating activity, specifically for the treatment of AIDS and ARC (abstract). Weiner et al. disclose lipid vesicles containing a biologically active agent (col. 2, lines 39-40). Lipid vesicles are also known as liposomes (col. 1, line 9). The biologically active agent includes inositol hexaphosphate (claim 11). Inositol hexaphosphate is a polyphosphate (col. 4, lines 10-11). It would have been obvious to one of ordinary skill

in the art to have incorporated polyphosphates having a chain length of greater than three phosphate units into liposomes since liposomes may comprise other therapeutic agents and polyphosphates with a chain length of more than 3 phosphate units are suitable therapeutic agents that are useful as antiviral agents with immunomodulating activity, specifically for the treatment of AIDS and ARC as taught by Schroeder et al. Furthermore, it would have been obvious to one of ordinary skill in the art that polyphosphates with a chain length of more than 3 phosphate units may be incorporated into liposomes since liposomes comprising polyphosphate as active agents are known as taught by Weiner et al.

This is a provisional nonstatutory double patenting rejection.

Conclusion

Claims 1-24 are rejected.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TRACY LIU whose telephone number is (571)270-5115. The examiner can normally be reached on M-F 8:30 am to 5:00 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, Frederick Krass can be reached on 571-272-0580. 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.

/TRACY LIU/
Examiner, Art Unit 1612

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Honigman Miller Schwartz and Cohn LLP/Ipsen
350 East Michigan Avenue, Suite 300
Kalamazoo, MI 49007

EXAMINER
LIU, TRACY

ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
10/04/2017	ELECTRONIC

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

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

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

patents@honigman.com
lzerby@honigman.com
arhoades@honigman.com

Office Action Summary	Application No. 15/364,021	Applicant(s) HONG ET AL.	
	Examiner TRACY LIU	Art Unit 1612	AIA (First Inventor to File) Status No

-- 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 *07/10/2017*.

☐ 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) *1-24* is/are pending in the application.

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

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-24* 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 *11/29/2016* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

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

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

Priority under 35 U.S.C. § 119

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

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

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

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

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

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

Attachment(s)

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

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

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

4) ☐ Other: _____.

DETAILED ACTION

The present application is being examined under the pre-AIA first to invent provisions. Claims included in the prosecution are claims 1-24.

Applicants' arguments, filed 07/10/2017, have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 103

The following is a quotation of pre-AIA 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, 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.

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 pre-AIA 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.

1. Claims 1, 2, 10 and 11 is/are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Rahman et al. (WO 03/030864, Apr. 17, 2003) in view of Schroeder et al. (DE 4,320,597, Jan. 5, 1995), Weiner et al. (US 4,397,846, Aug. 9, 1983) and Bolotin et al. (US 2004/0156891, Aug. 12, 2004).

Rahman et al. disclose a therapeutic composition comprising liposome entrapped irinotecan (abstract). Any suitable liposome-forming material can be used in the liposome. Suitable liposome-forming compounds include phospholipid, phosphatidyl choline (i.e. lecithin) and cholesterol (page 4, lines 7-9). The liposome, once formed, can be filtered through suitable filters to control their size distribution. The liposome can be filtered through a 100 nm filter to obtain a liposome having a diameter of about 100 nm or less (page 3, lines 22-28). Other therapeutic agents can be used in combination with irinotecan (page 7, lines 4-5). The composition is used to treat cancer (abstract).

Rahman et al. differ from the instant claims insofar as not disclosing wherein the liposome comprises a polyphosphate having 13-18 phosphate units per polyphosphate molecule.

However, Schroeder et al. disclose the use of polyphosphates having a chain length of greater than three phosphate units as a medicament (claim 1). Polyphosphates with a chain length of more than 3 phosphate units are useful as antiviral agents with immunomodulating activity, specifically for the treatment of AIDS and ARC (abstract).

Weiner et al. disclose lipid vesicles containing a biologically active agent (col. 2, lines 39-40). Lipid vesicles are also known as liposomes (col. 1, line 9). The biologically active agent includes inositol hexaphosphate (claim 11). Inositol hexaphosphate is a polyphosphate (col. 4, lines 10-11).

It would have been *prima facie* obvious to one of ordinary skill in the art to have incorporated polyphosphates having a chain length of greater than three phosphate units into the liposome of Rahman et al. since the liposome may comprise other therapeutic agents and polyphosphates with a chain length of more than 3 phosphate units are suitable therapeutic agents that are useful as antiviral agents with immunomodulating activity, specifically for the treatment of AIDS and ARC as taught by Schroeder et al. It would have been obvious to one of ordinary skill in the art that polyphosphates with a chain length of more than 3 phosphate units may be incorporated into liposomes since liposomes comprising polyphosphate as active agents are known as taught by Weiner et al.

The combined teachings of Rahman et al., Schroeder et al., and Weiner et al. do not disclose wherein the composition has a mole ratio of irinotecan to lipid between 0.15:1 to 1.5:1.

However, Bolotin et al. disclose a liposomal composition comprising an analgesic drug (claim 1). The molar ratio of encapsulated analgesic drug to lipid in said liposomal analgesic composition is at least 1.0 (claim 6).

It would have been prima facie obvious to one of ordinary skill in the art to have the mole ratio of irinotecan to lipid to be at least 1.0 since at least 1.0 is an effective drug:lipid mole ratio for liposomes comprising drugs as taught by Bolotin et al.

In regards to instant claim 10 reciting wherein the liposomes have a mean size of 112±15.5 nm and 112.3±15.5 nm, respectively, measured by QELS, Rahman et al. disclose wherein irinotecan liposomes have a size of 100 nm. Thus, it would have been obvious to one of ordinary skill in the art to have formulated a liposome of such size when measured with a variety of liposomal measuring techniques, such as QELS.

2. Claims 3, 4 and 13 is/are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Rahman et al. (WO 03/030864, Apr. 17, 2003) in view of Schroeder et al. (DE 4,320,597, Jan. 5, 1995), Weiner et al. (US 4,397,846, Aug. 9, 1983), Bolotin et al. (US 2004/0156891, Aug. 12, 2004) and further in view of Gupta et al. (WO 2000/009071, Feb. 24, 2000).

The teachings of Rahman et al., Schroeder et al, Weiner et al. and Bolotin et al. are discussed above. Rahman et al., Schroeder et al, Weiner et al. and Bolotin et al. do not disclose wherein the lecithin and cholesterol are in a 3:2 mole ratio and wherein the liposome comprises DSPC, wherein DSPC and cholesterol are in a 3:2 mole ratio.

However, Gupta et al. disclose a liposomal formulation useful in treatment of cancer and other proliferative diseases. The formulation comprises phospholipids and/or sterols both in molar ratio of 1-15 (claim 1). Suitable phospholipids include distearoyl phosphatidyl choline (page 5, line 23).

It would have been *prima facie* obvious to one of ordinary skill in the art to have incorporated distearoyl phosphatidyl choline (DSPC) into the liposome of Rahman et al. since distearoyl phosphatidyl choline is a known liposome-forming compound as taught by Gupta et al.

It would have been *prima facie* obvious to one of ordinary skill in the art to have lecithin:cholesterol or distearoyl phosphatidyl choline:cholesterol in a molar ratio ranging from 1-15 since is an effective molar ratio of phospholipids and sterols to formulate a liposome for treating cancer as taught by Gupta et al.

3. Claims 5-7, 12, 14 and 15 is/are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Rahman et al. (WO 03/030864, Apr. 17, 2003) in view of Schroeder et al. (DE 4,320,597, Jan. 5, 1995), Weiner et al. (US 4,397,846, Aug. 9, 1983), Bolotin et al. (US 2004/0156891, Aug. 12, 2004), Gupta et al. (WO 2000/009071, Feb. 24, 2000) and further in view of Woodle et al. (US 5,013,556, May 7, 1991).

The teachings of Rahman et al., Schroeder et al, Weiner et al. and Bolotin et al. are discussed above. Rahman et al., Schroeder et al, Weiner et al. and Bolotin et al. do not disclose wherein the liposome comprises an amphipathic polymer comprising a polyethylene glycol-lipid and wherein the grams of irinotecan to moles of phospholipid is in the ratio of 0.15:1 to 0.55:1.

However, Woodle et al. disclose a liposome composition which contains an amphipathic lipid derivatized with a polyalkylether, as exemplified by phosphatidylethanolamine derivatized with polyethylene glycol. The derivatized lipid

enhances the circulation time of the liposome several folds (abstract). The polyethylene glycol has a molecular weight between about 1,000 to 5,000 daltons (claim 21). The liposome contain 10-40 mole percent cholesterol, 40-85 mole percent neutral phospholipid and 5-15 mole percent phospholipid derivatized with polyethylene glycol (claim 9).

It would have been *prima facie* obvious to one of ordinary skill in the art to have incorporated phosphatidylethanolamine derivatized with polyethylene glycol into the liposome of Rahman et al. since phosphatidylethanolamine derivatized with polyethylene glycol enhances the circulation time of liposomes as taught by Woodle et al.

It would have been *prima facie* obvious to one of ordinary skill in the art for the grams of irinotecan to moles of phospholipid be in the ratio of 0.5:1 since Rahman et al. disclose wherein the liposome comprises 0.1 to 50 weight percent irinotecan and Woodle et al. disclose wherein liposomes may comprise 50 mole percent phospholipid. Thus, assuming a 100 g liposome, the liposome may comprise 25 g irinotecan and 50 mole percent phospholipid, thus having a 0.5:1 ratio of grams of irinotecan to moles of phospholipid.

4. Claim 8 is/are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Rahman et al. (WO 03/030864, Apr. 17, 2003) in view of Schroeder et al. (DE 4,320,597, Jan. 5, 1995), Weiner et al. (US 4,397,846, Aug. 9, 1983), Bolotin et al. (US

2004/0156891, Aug. 12, 2004), Gupta et al. (WO 2000/009071, Feb. 24, 2000) and further in view of Cullis et al. (US 6,417,326, Jul. 9 , 2002).

The teachings of Rahman et al., Schroeder et al, Weiner et al. and Bolotin et al. are discussed above. Rahman et al., Schroeder et al, Weiner et al. and Bolotin et al. do not disclose the liposome comprises N-(methoxy-poly(ethylene glycol)-oxycarbonyl)-distearoylphosphatidylethanolamine (PEG-DSPE).

However, Cullis et al. disclose liposomes comprising DSPE-PEG_{2000} (Fig. 8).

It would have been *prima facie* obvious to one of ordinary skill in the art to have incorporated DSPE-PEG_{2000} into the liposome of Rahman et al. since DSPE-PEG_{2000} is a known liposome-forming compound as taught by Cullis et al.

In regards to instant claim 8 reciting wherein the mole ratio of DSPC, cholesterol, and PEG-DSPE is 3:2:0.015, Gupta et al. disclose wherein the mole ratio of phospholipids and sterols in liposomes is from 1-15.

5. Claims 9 and 16 is/are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Rahman et al. (WO 03/030864, Apr. 17, 2003) in view of Schroeder et al. (DE 4,320,597, Jan. 5, 1995), Weiner et al. (US 4,397,846, Aug. 9, 1983), Bolotin et al. (US 2004/0156891, Aug. 12, 2004), Gupta et al. (WO 2000/009071, Feb. 24, 2000) and further in view of Hardee et al. (US 6,083,923, Jul. 4, 2000).

The teachings of Rahman et al., Schroeder et al, Weiner et al., Bolotin et al. and Gupta et al. are discussed above. Rahman et al., Schroeder et al, Weiner et al., Bolotin et al. and Gupta et al. do not disclose the liposome comprises MPEG-2000-DSPE.

However, Hardee et al. disclose liposomes comprising DSPE-$MPEG_{2000}$ (col. 28, lines 2-3).

It would have been *prima facie* obvious to one of ordinary skill in the art to have incorporated DSPE-$MPEG_{2000}$ into the liposome of Rahman et al. since DSPE-$MPEG_{2000}$ is a known liposome-forming compound as taught by Hardee et al.

In regards to instant claims 9 and 16 reciting wherein the mole ratio of DSPC, cholesterol, and MPEG-2000-DSPE is 3:2:0.015, Gupta et al. disclose wherein the mole ratio of phospholipids and sterols in liposomes is from 1-15.

6. Claims 17-21 is/are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Rahman et al. (WO 03/030864, Apr. 17, 2003) in view of Schroeder et al. (DE 4,320,597, Jan. 5, 1995), Weiner et al. (US 4,397,846, Aug. 9, 1983), Bolotin et al. (US 2004/0156891, Aug. 12, 2004) and further in view of Steffen et al. (US 4,649,155, Mar. 10, 1987).

The teachings of Rahman et al., Schroeder et al, Weiner et al. and Bolotin et al. are discussed above. Rahman et al., Schroeder et al, Weiner et al. and Bolotin et al. do not disclose wherein the ratio of irinotecan to phospholipid is 200 g per mol phospholipid, 300 g per mol phospholipid, 400 g per mol phospholipid, 500 g per mol phospholipid or 550 g per mol phospholipid.

However, Steffen et al. disclose an injectable aqueous micellar solution comprising vitamin E, a phospholipid and a cholanic acid or salt thereof. The solution contains at least about 100 g of vitamin E per mol of phospholipid (claim 1).

It would have been *prima facie* obvious to one of ordinary skill in the art to have the ratio of irinotecan to phospholipid be at least about 100 g per mol of phospholipid since this is an effective amount of active agent to phospholipid ratio as taught by Steffen et al.

7. Claim 22 is/are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Rahman et al. (WO 03/030864, Apr. 17, 2003) in view of Schroeder et al. (DE 4,320,597, Jan. 5, 1995), Weiner et al. (US 4,397,846, Aug. 9, 1983), Hardee et al. (US 6,083,923, Jul. 4, 2000) and Steffen et al. (US 4,649,155, Mar. 10, 1987).

Rahman et al. disclose a therapeutic composition comprising liposome entrapped irinotecan (abstract). Any suitable liposome-forming material can be used in the liposome. Suitable liposome-forming compounds include phospholipid, phosphatidyl choline (i.e. lecithin) and cholesterol (page 4, lines 7-9). The liposome, once formed, can be filtered through suitable filters to control their size distribution. The liposome can be filtered through a 100 nm filter to obtain a liposome having a diameter of about 100 nm or less (page 3, lines 22-28). Other therapeutic agents can be used in combination with irinotecan (page 7, lines 4-5). The composition is used to treat cancer (abstract).

Rahman et al. differ from the instant claims insofar as not disclosing wherein the liposome encapsulates a polyphosphate.

However, Schroeder et al. disclose the use of polyphosphates having a chain length of greater than three phosphate units as a medicament (claim 1). Polyphosphates with a chain length of more than 3 phosphate units are useful as

antiviral agents with immunomodulating activity, specifically for the treatment of AIDS and ARC (abstract).

Weiner et al. disclose lipid vesicles containing a biologically active agent (col. 2, lines 39-40). Lipid vesicles are also known as liposomes (col. 1, line 9). The biologically active agent includes inositol hexaphosphate (claim 11). Inositol hexaphosphate is a polyphosphate (col. 4, lines 10-11).

It would have been *prima facie* obvious to one of ordinary skill in the art to have incorporated polyphosphates having a chain length of greater than three phosphate units into the liposome of Rahman et al. since the liposome may comprise other therapeutic agents and polyphosphates with a chain length of more than 3 phosphate units are suitable therapeutic agents that are useful as antiviral agents with immunomodulating activity, specifically for the treatment of AIDS and ARC as taught by Schroeder et al. It would have been obvious to one of ordinary skill in the art that polyphosphates with a chain length of more than 3 phosphate units may be incorporated into liposomes since liposomes comprising polyphosphate as active agents are known as taught by Weiner et al.

The combined teachings of Rahman et al., Schroeder et al., and Weiner et al. do not disclose wherein the liposome comprises a PEGylated lipid.

However, Hardee et al. disclose liposomes comprising DSPE-MPEG$_{2000}$ (col. 28, lines 2-3).

It would have been *prima facie* obvious to one of ordinary skill in the art to have incorporated DSPE-$MPEG_{2000}$ into the liposome of Rahman et al. since DSPE-$MPEG_{2000}$ is a known liposome-forming compound as taught by Hardee et al.

The combined teachings of Rahman et al., Schroeder et al., Weiner et al. and Hardee et al. do not disclose wherein the composition has a 465.6±26.5 mg irinotecan per mmol phospholipid.

However, Steffen et al. disclose an injectable aqueous micellar solution comprising vitamin E, a phospholipid and a cholanic acid or salt thereof. The solution contains at least about 100 g of vitamin E per mol of phospholipid (claim 1).

It would have been *prima facie* obvious to one of ordinary skill in the art to have at least about 100 g irinotecan per mol of phospholipid since this is an effective amount of active agent to phospholipid ratio as taught by Steffen et al.

In regards to instant claim 22 reciting wherein the liposomes have a mean size of 112.3±15.5 nm, respectively, measured by QELS, Rahman et al. disclose wherein irinotecan liposomes have a size of 100 nm. Thus, it would have been obvious to one of ordinary skill in the art to have formulated a liposome of such size when measured with a variety of liposomal measuring techniques, such as QELS.

8. Claims 23 and 24 is/are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Rahman et al. (WO 03/030864, Apr. 17, 2003) in view of Schroeder et al. (DE 4,320,597, Jan. 5, 1995), Weiner et al. (US 4,397,846, Aug. 9, 1983), Hardee

et al. (US 6,083,923, Jul. 4, 2000), Steffen et al. (US 4,649,155, Mar. 10, 1987) and further in view of Gupta et al. (WO 2000/009071, Feb. 24, 2000).

The teachings of Rahman et al., Schroeder et al.,Weiner et al., Hardee et al., and Steffen et al. are discussed above. Rahman et al., Schroeder et al.,Weiner et al., Hardee et al., and Steffen et al. do not disclose wherein the liposome comprises DSPC and wherein the DSPC and cholesterol are in a mole ratio of 3:2 and the DSPC, cholesterol and MPEG-2000-DSPE is in a mole ratio of 3:2:0.015.

However, Gupta et al. disclose a liposomal formulation useful in treatment of cancer and other proliferative diseases. The formulation comprises phospholipids and/or sterols both in molar ratio of 1-15 (claim 1). Suitable phospholipids include distearoyl phosphatidyl choline (page 5, line 23).

It would have been *prima facie* obvious to one of ordinary skill in the art to have incorporated distearoyl phosphatidyl choline (DSPC) into the liposome of Rahman et al. since distearoyl phosphatidyl choline is a known liposome-forming compound as taught by Gupta et al.

It would have been *prima facie* obvious to one of ordinary skill in the art to have distearoyl phosphatidyl choline:cholesterol or DSPC:cholesterol:MPEG-2000-DSPE in a molar ratio ranging from 1-15 since is an effective molar ratio of phospholipids and sterols to formulate a liposome for treating cancer as taught by Gupta et al.

Response to Arguments

Applicant argues that the polyphosphates required by the present claims are polymeric oxyanions formed from tetrahedral PO_4 structural units linked together by sharing oxygen atoms (Structure A in Figure 1). Whereas the structures described as polyphosphates by Weiner are not phosphate units linked together to form polymers as in Structure A of Figure 1, but are rather polyphorylated polyols made by the phosphorylation of inositol.

The Examiner does not find Applicant's argument to be persuasive. The instant specification does not define the claimed polyphosphate as polymeric oxyanions formed from tetrahedral PO_4 structural units linked together by sharing oxygen atoms. While the instant specification discloses examples comprising such polyphosphate, examples are not definitions. Therefore, since the instant specification does not define polyphosphate as polymeric oxyanions formed from tetrahedral PO_4 structural units linked together by sharing oxygen atoms, the claimed polyphosphate is given its broadest reasonable interpretation. Inositol hexaphosphate is a polyphosphate because Weiner discloses wherein inositol hexaphosphate is a polyphosphate in col. 4, lines 10-11. The instant specification also discloses wherein inositol hexaphosphate is a polyphosphate in paragraph [0079] of the instant specification. Therefore, Weiner does not teach away from the claimed invention and as discussed obvious it would have been obvious to have incorporated a polyphosphate into a liposome since Weiner discloses a liposome comprising inositol hexaphosphate, which is a polyphosphate.

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 1-24 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-10 of copending Application No. **15/363,978**, claims 1-10 of copending Application No. **15/363,761**, claims 1-19 of copending Application No. **15/363,923** in view of Rahman et al. (WO 03/030864, Apr. 17, 2003), Schroeder et al. (DE 4,320,597, Jan. 5, 1995) and Weiner et al. (US 4,397,846, Aug. 9, 1983). The pending claims differ from the copending claims insofar as reciting therein the liposome have a mean size of 112.3±15.5 nm measured by QELS. However, Rahman et al. disclose wherein irinotecan liposomes have a size of 100 nm. Thus, it would have been obvious to one of ordinary skill in the art to have formulated a liposome of such size when measured with a variety of liposomal measuring techniques, such as QELS, since 100 nm is an effective size for irinotecan

liposomes. Furthermore, the pending claims differ from the copending claims insofar as reciting a polyphosphate having 13-18 phosphate units per polyphosphate molecule. However, Schroeder et al. disclose the use of polyphosphates having a chain length of greater than three phosphate units as a medicament (claim 1). Polyphosphates with a chain length of more than 3 phosphate units are useful as antiviral agents with immunomodulating activity, specifically for the treatment of AIDS and ARC (abstract). Weiner et al. disclose lipid vesicles containing a biologically active agent (col. 2, lines 39-40). Lipid vesicles are also known as liposomes (col. 1, line 9). The biologically active agent includes inositol hexaphosphate (claim 11). Inositol hexaphosphate is a polyphosphate (col. 4, lines 10-11). It would have been obvious to one of ordinary skill in the art to have incorporated polyphosphates having a chain length of greater than three phosphate units into liposomes since liposomes may comprise other therapeutic agents and polyphosphates with a chain length of more than 3 phosphate units are suitable therapeutic agents that are useful as antiviral agents with immunomodulating activity, specifically for the treatment of AIDS and ARC as taught by Schroeder et al. Furthermore, it would have been obvious to one of ordinary skill in the art that polyphosphates with a chain length of more than 3 phosphate units may be incorporated into liposomes since liposomes comprising polyphosphate as active agents are known as taught by Weiner et al.

This is a provisional nonstatutory double patenting rejection.

Response to Arguments

Applicants respectfully defer these issues until the application is otherwise in condition for allowance. Since this has not occurred, the rejection is maintained.

Conclusion

Claims 1-24 are rejected.

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TRACY LIU whose telephone number is (571)270-5115. The examiner can normally be reached on M-F 8:30 am to 5:00 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, Frederick Krass can be reached on 571-272-0580. 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.

/TRACY LIU/
Examiner, Art Unit 1612

/FREDERICK KRASS/
Supervisory Patent Examiner, Art Unit 1612

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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Honigman Miller Schwartz and Cohn LLP/Ipsen
350 East Michigan Avenue, Suite 300
Kalamazoo, MICHIGAN 49007

EXAMINER	
BAEK, BONG-SOOK	

ART UNIT	PAPER NUMBER
1621	

NOTIFICATION DATE	DELIVERY MODE
02/16/2018	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):

arhoades@honigman.com
lzerby@honigman.com
patents@honigman.com

Office Action Summary	Application No. 15/375,039	Applicant(s) Bayever et al.	
	Examiner BONG-SOOK BAEK	Art Unit 1621	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 1/30/2018 .

☐ 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) 1-6,8,11,16-17,19-21,23,26 and 31-35 is/are pending in the application.

5a) Of the above claim(s) 1-6,8,11,16-17,19-21,23,26 and 32 is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 31 and 33-35 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 17 February 2017 is/are: a)☑ accepted or b)☐ objected to by the Examiner.

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

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

Priority under 35 U.S.C. § 119

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

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

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

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

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

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

Attachment(s)

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

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

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

4) ☐ Other: _____.

Notice of Pre-AIA or AIA Status

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

DETAILED ACTION

Election/Restrictions

Applicants' election of Group II, in the reply filed on 1/30/2018 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a))

Claims 1-6, 8, 11, 16, 17, 19-21, 23, 26, and 32 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Claims 31 and 33-35 are under examination in the instant office action.

Claim objections

Claim 31 is objected to because of the following informalities: A full name of "nal-IRI" should be given in claim 31 for clarification and then use its acronym thereafter.

Claim 35 is objected to because of the following informalities: typographical error. "80 mg/m2" in line 3 should be corrected to 80 mg/m^2.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a)(1) the claimed invention was patented, described in a printed publication, or in public use, on sale or otherwise available to the public before the effective filing date of the claimed invention.

Claim 31 is rejected under 35 U.S.C. 102(a)(1) as being anticipated by US 2014/0170075 (cited in the IDS filed on 2/17/2017).

US 2014/0170075 teaches a method for selecting and providing pharmaceutical treatment to a patient for a localized infectious, inflammatory, or neoplastic condition, the method comprising identifying one or more locations of infection, inflammation or neoplasia in a patient, and subsequently, obtaining at least one contrast-enhanced MRI image of a first location of the one or more locations, and subsequently, selecting an anti-infective, anti-inflammatory, or anti-neoplastic pharmaceutical agent and treating the patient with the selected pharmaceutical agent, wherein the contrast agent is ferumoxytol (FMX) which is intravenously administered at 5 mg/kg up to 510 mg/kg and wherein the pharmaceutical agent is a liposomal anti-neoplastic agent (abstract, [0019], [0020]claims 8-13). US 2014/0170075 also teaches that the liposomal therapeutic agent is MM-398 (irinotecan sucroseoctasulfate liposome injection) and the tumor is a non-small cell lung cancer (NSCLC) tumor, a triple negative breast cancer (TNBC) tumor (HER2 negative breast cancer), a colorectal cancer (CRC) tumor, a pancreatic cancer tumor, a small cell lung cancer tumor, a gastric cancer tumor, a cervical cancer tumor, a head and neck cancer, or Ewing's sarcoma (claims 14-16). US 2014/0170075 teaches that as FMX, which is a preparation of polyglucose sorbitol carboxymethylether coated magnetite (superparamagnetic iron oxide) nanoparticles ([0008]), has been demonstrated to be safe for intravenous administration to patients and is shown herein not to interfere with nanoliposome therapies if used as an imaging agent, even within 1-4 hours prior to administration of nanoliposomal therapeutics, these results indicate that FMX MRI allows for selection patients who will (or will

not) benefit from nanoliposomal therapy ([0105]). US 2014/0170075 further teaches that patients identified as having sites of pathology that are predicted to exhibit nanoparticle accumulation would be considered more likely to respond to nanoparticulate therapeutic agents and patients identified as having sites of pathology that are predicted not to exhibit nanoparticle accumulation would be considered less likely to respond to nanoparticulate therapeutic agents and treating patients in accordance with such identifications would avoid the administration of sub-optimal therapeutic treatments to patients in need of therapy ([0011]).

The reference specifically discloses a human clinical trial (ClinicalTrials.gov Identifier: NCT01770353) wherein patients with advanced solid tumors and multiple metastases were injected with FMX at 5 mg/kg, tumor samples of the patients were removed (tumor biopsies) after FMX injection, and the deposition amount of FMX in the tumor lesion was detected by staining the sample with Prussian blue, which is a dye specific for iron, and then the patients were infused with 80 mg/m^2 MM-398 and shows that the patents have tumor lesion with FMX uptake (see[0135], [0137], [0139], and Examples 8-10).

As such, the instant claim 31 is anticipated by US 2014/0170075.

Claim Rejections - 35 USC § 103

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

> A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102 of this title, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

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 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.

Claims 33-25 are rejected under 35 U.S.C. 103 as being unpatentable over US 2014/0170075 in view of Noble *et al.* (Cancer Res. 66(5): 2801-2806, 2006, cited in the IDS filed on 2/17/2017).

US 2014/0170075 teaches a method for selecting and providing pharmaceutical treatment to a patient for a localized infectious, inflammatory, or neoplastic condition, the method comprising identifying one or more locations of infection, inflammation or neoplasia in a patient, and subsequently, obtaining at least one contrast-enhanced MRI image of a first location of the one or more locations, and subsequently, selecting an anti-infective, anti-inflammatory, or anti-neoplastic pharmaceutical agent and treating the patient with the selected pharmaceutical agent, wherein the contrast agent is ferumoxytol (FMX) which is intravenously administered at 5 mg/kg up to 510 mg/kg and wherein the pharmaceutical agent is a liposomal anti-neoplastic agent (abstract, [0019], [0020]claims 8-13). US 2014/0170075 also teaches that the liposomal therapeutic agent is MM-398 (irinotecan sucroseoctasulfate liposome injection) and the tumor is a non-small cell lung cancer (NSCLC) tumor, a triple negative breast cancer (TNBC) tumor, a colorectal cancer (CRC) tumor, a pancreatic cancer tumor, a small cell lung cancer tumor, a

gastric cancer tumor, a cervical cancer tumor, a head and neck cancer, or Ewing's sarcoma ([0068] and claims 14-16). US 2014/0170075 teaches that as FMX has been demonstrated to be safe for intravenous administration to patients and is shown herein not to interfere with nanoliposome therapies if used as an imaging agent, even within 1-4 hours prior to administration of nanoliposomal therapeutics, these results indicate that FMX MRI allows for selection patients who will (or will not) benefit from nanoliposomal therapy ([0105]). US 2014/0170075 further teaches that patients identified as having sites of pathology that are predicted to exhibit nanoparticle accumulation would be considered more likely to respond to nanoparticulate therapeutic agents and patients identified as having sites of pathology that are predicted not to exhibit nanoparticle accumulation would be considered less likely to respond to nanoparticulate therapeutic agents and treating patients in accordance with such identifications would avoid the administration of sub-optimal therapeutic treatments to patients in need of therapy ([0011]).

US 2014/0170075 specifically discloses a human clinical trial (ClinicalTrials.gov Identifier: NCT01770353) wherein patients with advanced solid tumors and multiple metastases were injected with FMX at 5 mg/kg, tumor samples of the patients were removed (tumor biopsies) after FMX injection, and the deposition amount of FMX in the tumor lesion was detected by staining the sample with Prussian blue, which is a dye specific for iron, and then the patients were infused with 80 mg/m^2 MM-398 and shows that the patents have tumor lesion with FMX uptake (see[0135], [0137], [0139], and Examples 8-10).

The reference does not specifically disclose the treatment of breast cancer with active brain metastasis.

Noble *et al.* teaches that convection-enhanced delivery of nanoliposomal CPT-11 (irinotecan) greatly prolonged tissue residence while also substantially reducing toxicity, resulting in a highly effective treatment strategy in preclinical brain tumor models (abstract).

It would have been prima facie obvious to one of ordinary skill in the art before the effective filing date of the claimed invention to use nanoliposomal irinotecan such as MM-398 for treating breast cancer with active brain metastasis because of the following reasons. As stated above, nanoliposomal irinotecan such as MM-398 was known to be effective for treating breast cancer with active metastatic lesion and a head and neck cancer as evidenced by US 2014/0170075. Also, Noble *et al.* teaches that irinotecan in a nanoliposome is suitable for treating brain tumor. Thus, one of ordinary skill in the art would have been motivated to use the nanoliposomal irinotecan such as MM-398 taught by US 2014/0170075 in the treatment of breast cancer with active brain metastasis on the reasonable expectation that it would effectively treat both breast and brain tumor lesions.

Claims 33-35 are rejected under 35 U.S.C. 103 as being unpatentable over US 2014/0170075 in view of US2013/0274281.

US 2014/0170075 as applied *supra* are herein applied for the same teachings in their entirety.

The reference does not specifically disclose the treatment of breast cancer with active brain metastasis.

US2013/0274281 teaches the use of irinotecan in combination with 4-iodo-3-nitrobenzamide for the treatment of locally advanced or metastatic breast cancer or breast cancer

with brain metastases wherein the breast cancer can be HER2 positive or negative (abstract and claims 4-6).

It would have been prima facie obvious to one of ordinary skill in the art before the effective filing date of the claimed invention to use the nanoliposomal irinotecan such as MM-398 taught by US 2014/0170075 in the treatment of breast cancer with active brain metastasis because US 2014/0170075 already teaches that the nanoliposomal irinotecan such as MM-398 is useful for treating breast cancer with active metastatic lesion and irinotecan was also known to be suitable for treating breast cancer with active brain metastasis as evidenced by US2013/0274281. One of ordinary skill in the art would have reasonably expected that the nanoliposomal irinotecan such as MM-398, which is generally useful for treating breast cancer as evidenced by US 2014/0170075, would also be useful for treating subtypes of breast cancer including breast cancer with active brain metastasis in the absence of evidence to the contrary.

Double Patenting Rejection

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 obviousness-type 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); and *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 a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 31 and 33-35 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 4-14 of copending Application No. 14/964571.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of '571 application are drawn to a method of treating breast cancer with active brain metastasis comprising intravenously administrating MM-398 in an amount effective to administer the amount of irinotecan present in a 80 mg/m2 dose of irinotecan hydrochloride trihydrate to a patient having a tumor lesion with a ferumoxytol tumor lesion uptake of at least 32.6 mcg/mL one hour after intravenous administration of ferumoxytol (FMX). The claims of '571 do not specifically recite the steps of detecting the amount of FMX as recited in claim 31. However, it would have been obvious to perform a detection method of FMX deposition for determining the FMX uptake in the tumor lesion in order to identify whether the

patient has required uptake amount as disclosed in the specification of '571 application ([0344]). Thus, the claims of the instant application would have been obvious over those of the '571 application. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BONG-SOOK BAEK whose telephone number is 571-270-5863. The examiner can normally be reached 9:00AM-6:00PM Monday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Melenie McCormick can be reached on 571-272-8037. 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.

/BONG-SOOK BAEK/
Primary Examiner, Art Unit 1621

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/403,441	01/11/2017	Eliel Bayever	263266-411944	2070

139696 7590 12/21/2017

Honigman Miller Schwartz and Cohn LLP/Ipsen
350 East Michigan Avenue, Suite 300
Kalamazoo, MI 49007

EXAMINER
PACKARD, BENJAMIN J

ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
12/21/2017	ELECTRONIC

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

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

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

patents@honigman.com
lzerby@honigman.com
arhoades@honigman.com

Office Action Summary	Application No. 15/403,441	Applicant(s) BAYEVER ET AL.	
	Examiner BENJAMIN PACKARD	Art Unit 1612	AIA (First Inventor to File) Status Yes

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

Period for Reply

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

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

Status

1)☐ Responsive to communication(s) filed on _____.

☐ 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) *1-20* is/are pending in the application.

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

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-20* 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 _____ 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 *4pgs (1/11/17)*.

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

4) ☐ Other: _____.

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

Claim Rejections - 35 USC § 103

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.

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

> A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

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 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.

This application currently names joint inventors. In considering patentability of the claims the examiner presumes that the subject matter of the various claims was commonly owned as of the effective filing date of the claimed invention(s) absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and effective filing dates of each claim that was not commonly owned as of the effective filing date of the later invention in order for the examiner to consider the applicability of 35 U.S.C. 102(b)(2)(C) for any potential 35 U.S.C. 102(a)(2) prior art against the later invention.

Claims 1-20 is/are rejected under 35 U.S.C. 103 as being unpatentable over Yoo et al (British Journal of Cancer, 2009, 101, 1658-1663) in view of Tsai et al (Journal of Gastrointestinal Oncology, 2011, Vol 2, No 3, 185-194).

Yoo teaches a method of treating metastatic pancreatic cancer refractory to gemcitabine therapy (abstract) though administration of a drug combination regimen comprising irinotecan (70mg/m2), leucovorin (400 mg/m2) and 5-fluorouraccill (2000mg/m2) (pg 1659, col 2, ¶ 3). Yoo further teaches administration of 5-FU over a 46 hr period with the entire regimen repeated every two weeks.

Yoo does not teach liposomal irinotecan.

Tsai et al teaches liposomal delivery of irinotecan for pancreatic cancer having an enhanced drug delivery comparted to non-liposomal agents. (pg 189 ¶ 3).

It would have been obvious to one of ordinary skill in the art to modify the treatment of Yoo based on the teaching of Tsai to include the liposomal form of irinotecan for improved delivery.

While the instant claims note the CA 19-9 levels, Examiner notes the treatment disclosed is directed to all patients, which would include patients of this subpopulation having the marker present.

Further, where the racemic forms are claimed, it would have bene obvious that the composition would include both where the generic form is disclosed.

Obvious Type 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 1-20 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-35 of U.S. Patent No. 9,452,162. Although the claims at issue are not identical, they are not patentably distinct from each other because the patient population of the patent is directed to patients having specific UGT1A1*28 allele profiles. This is obvious as the instant claims are directed to a different marker that overlaps, given the same treatment of the same condition is claimed.

The claims are rejected for the reasons recited above with regards to the following patents as well:

Claim 1-27 of US Patent No. 9339497

Claim 1-29 of US Patent No. 9364473

Claim 1-30 of US Patent No. 9492442

Claim 1-24 of US Patent No. 9717724

Claims 1-20 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-20 of copending Application No. 14/964571 Although the claims at issue are not identical, they are not patentably distinct from each other because they are directed to similar methods.

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

Claims 1-20 are further provisionally rejected over the following:

Claims 2, 4-15, 18-22 of copending Application No. 15/241106. Includes an additional agent, but makes obvious the components instantly claimed.

Claims 2-3, 6, 10-15 of copending Application No. 15/341377 in view of Yoo et al (British Journal of Cancer, 2009, 101, 1658-1663). '377 teaches administration of liposomal irinotecan and Yoo et al teaches the additional claimed agents, as discussed above.

Claims 12-34 of 15/341619 in view of Yoo et al (British Journal of Cancer, 2009, 101, 1658-1663). '377 teaches administration of liposomal irinotecan and Yoo et al teaches the additional claimed agents, as discussed above.

Claims 1-20 of 15/652513 in view of Yoo et al (British Journal of Cancer, 2009, 101, 1658-1663). '377 teaches administration of liposomal irinotecan and Yoo et al teaches the additional claimed agents, as discussed above.

Claims 1-20 of 15/664930.

Claims 1-20 of 15/809815. Includes an additional agent, but makes obvious the components instantly claimed.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BENJAMIN PACKARD whose telephone number is (571)270-3440. The examiner can normally be reached on M-R 8-6 EST.

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, Frederick Krass can be reached on 571-272-0580. 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.

/BENJAMIN PACKARD/
Primary Examiner, Art Unit 1612

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/645,645	07/10/2017	Daryl C. Drummond	263266-415164	1010

139696 7590 12/01/2017

Honigman Miller Schwartz and Cohn LLP/Ipsen
350 East Michigan Avenue, Suite 300
Kalamazoo, MI 49007

EXAMINER	
SHOMER, ISAAC	

ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
12/01/2017	ELECTRONIC

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

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

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

patents@honigman.com
lzerby@honigman.com
arhoades@honigman.com

Office Action Summary	Application No. 15/645,645	Applicant(s) Drummond et al.	
	Examiner ISAAC SHOMER	Art Unit 1612	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 10 July 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) 1-20 is/are pending in the application.

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

6)☐ Claim(s) _____ is/are allowed.

7)☑ Claim(s) 1-20 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 _____ 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: _____ .

DETAILED CORRESPONDENCE

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.

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.

Status of Claims

Claims 1-20 are pending and subject to substantive examination.

Claim Interpretation

With regard to claim language, the examiner notes that the claims make use of language in parentheses. The examiner clarifies that the language inside the parentheses are not understood to refer to optional limitations. In contrast, the parentheses are used for the following reasons:

A) To clarify an abbreviation, e.g. SOS for sucrose octasulfate, as of the second line of claim 1.

B) To express a statistical deviance (e.g. as of claim 1, third line).

C) To express a limitation that would result in a sentence that reads in a grammatically unpleasant manner had the parentheses not been used (e.g. the limitation drawn to "(with respect to total phospholipids)" on the fourth and fifth lines of claim 1.

As such, the inclusion of parentheses in claims is not understood to render the claims indefinite.

Additionally, the examiner understands the abbreviation "TEA" and "DEA", (e.g. as in claim 16, as well as elsewhere in the claims, to refer to both trimethylamine and diethylamine.

Claim Rejections - 35 USC § 112(b) – Indefiniteness

The following is a quotation of 35 U.S.C. 112(b):
(b) CONCLUSION.—The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), second paragraph:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 12-15 are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention.

Claims 12-15 recite "the liposomal irinotecan composition of any claim 1." It is unclear what is meant by "any claim 1." For the purposes of examination under prior art, these claims are understood to depend from claim 1.

Claim 15 is rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention.

Claim 15, part (c), recites "removing ions derived from TEA_8SOs that are outside the liposomes. It is unclear what is meant by ions derived from TEA_8SOS. For the purposes of examination under prior art, said ions are understood to refer to triethylammonium ions $(HN(CH_3)_3)^+$ or the SOS anion, which has a charge of -8. Chemical derivations of these ions comprising covalent bonding other than addition or removal of a H^+ ion (i.e. acid-base reactions) are not understood to be included in the claim scope.

Cited Art

As relevant art, the examiner cites Drummond et al. (WO 2017/066726 A1). Drummond et al. (hereafter referred to as Drummond '726) is drawn to storage stable liposomal irinotecan compositions. Drummond '726 was published on 20 April 2017. This is later than the earliest effective filing date of the instant application of 21 October 2016. As such, Drummond is not prior art under AIA 35 U.S.C. 102(a)(1).

Drummond '720 has an earliest effective filing date of 16 October 2015, based upon provisional applications to which Drummond '720 claims benefit. This is earlier than the earliest effective filing date of the instant application of 21 October 2016. Nevertheless, Drummond '720 has the same inventors as the instant application. As

such, despite the earlier filing date, Drummond '720 is not prior art under AIA 35 U.S.C. 102(a)(2) as it does not name another inventor. See MPEP 2154.01(c).

Close Prior Art

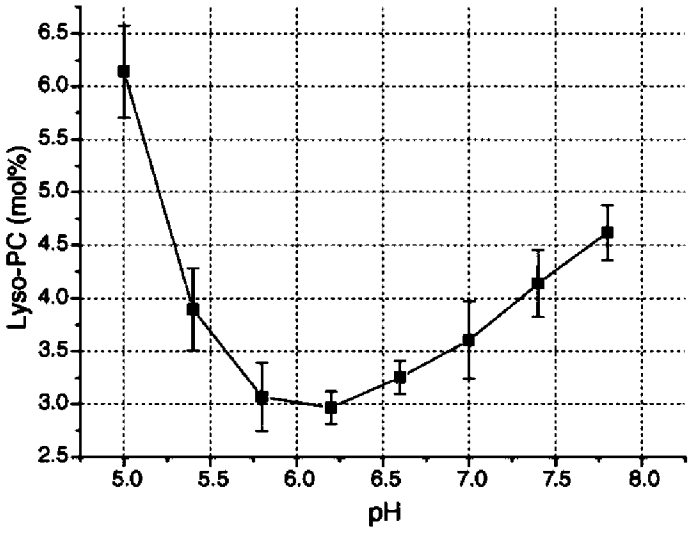
The instant claims are drawn to a liposomal composition comprising irinotecan and sucrose octasulfate. As close and relevant prior art, the examiner cites Drummond et al. (US 2007/0110798 A1) and Hong et al. (US 2007/0116753 A1). The following reasons are provided by the examiner explaining why the instant claims have not been rejected as anticipated by these references or obvious over these references. Also cited by the examiner is Saetern et al. (International Journal of Pharmaceutics, Vol. 288, 2005, pages 73-80).

The examiner notes that the reasons for non-rejection provided here are similar to the reasons provided in the notice of allowance for case 15/331,648 on 10 April 2017 and in case 15/331,318 on 27 April 2017. Both of these cases were abandoned after a notice of allowance for lack of payment of the issue fee.

Liposomes are known to suffer from degradation when in storage. One such form of degradation involves the hydrolysis of phosphatidylcholine, which is a phospholipid molecule with two chains that makes up the structural of the bilayer of the liposome, to lysophosphatidylcholine. Such lysophosphatidylcholine is understood to have poor stability in the liposome bilayer, and a bilayer comprising lysophosphatidylcholine is subject to degradation. The instantly claimed invention is drawn to a liposome that has unexpectedly greater storage stability than the liposomes of the Drummond and Hong

prior art references cited above. As such, the instantly claimed invention differs from the composition of the prior art for the following reasons:

A) pH Range: First, the instantly claimed liposome is stored in a medium wherein the pH is 7.0 to 7.5 (as in claims 1 and 20) and about 7.3 in claim 15. Hong teaches that the liposome should be stored at a pH of between 6.0 and 7.5, with a pH of 6.5 as most optimal, as of Hong, paragraph 0115. However, additional relevant prior art shows that storage of a liposome in a pH of about 6.25 to 6.5 has the greatest storage stability, and that deviation from pH 6.25-6.5 results in more degradation during storage as compared to storage at pH 6.5. In support of this position, the examiner cites Saetern et al. (International Journal of Pharmaceutics, Vol. 288, 2005, pages 73-80). Saetern et al. (hereafter referred to as Saetern), teaches the following graph regarding degradation of phosphatidylcholine to lysophosphatidylcholine, as of page 77, right column, Figure 5, which is reproduced below.



As such, the data of Saetern indicates that a pH of about 6.25 provides the greatest stability of a phosphatidylcholine containing liposome. The examiner also notes

that the Saetern publication is especially relevant here because Saetern is drawn to encapsulating camptothecin as a drug, and the instant claims are drawn to a liposome that encapsulates irinotecan as a drug, wherein irinotecan is a derivative of camptothecin.

However, in the instant specification, applicant has presented data showing that a pH range of 7.0 to 7.5 unexpectedly provides increased stability as compared to a pH of about 6.5. In support of this position, the examiner cites table 1 on pages 22 and 23 of the instant specification.

Instant table 1 discloses that a liposome at a pH of 6.5 and a sulfate group concentration of 0.45 M shows 14.6 mol% or 19.5 mol% of lysophosphatidylcholine after 6 months, as of samples #6 and #1 respectively. In contrast, a sample with a pH of 7.25 and an identical sucrose octasulfate concentration of 0.45 M shows only about 7.1 mol% or 7.4 mol% of lyosphosphatidylcholine after 6 months of storage, as of page 21, Table 1, items #5 and #7 respectively. As a greater percentage of lysophosphatidylcholine indicates a less stable liposome, the data presented in Table 1 show an increase in stability when the pH of a sucrose octasulfate containing irinotecan liposome is raised from 6.5 to 7.25.

This increase in stability with increase in pH is at odds with the teachings of the prior art, which indicate that a lower pH of 6.25 to 6.5 is optimal for achieving stability of the liposome. As applicant has shown that the claimed pH range is critical for achieving increased stability, this is understood to be evidence of non-obviousness. See MPEP 2144.05(III)(A).

B) Sucrose Octasulfate Loading Concentration: In the instantly claimed product-by-process, sucrose octasulfate was loaded in a concentration such that the sulfate groups are present in a concentration of 0.4 to 0.5 M, as of part (a) of claim 1. In contrast, in the examples of the prior art, the concentration of sucrose octasulfate inside the liposome was at minimum 0.65 M to about 1.0 M, e.g. as of Hong, page 11, end of paragraph 0104.

Data in the instant application show that loading with a lower level of sucrose octasulfate with a sulfate group concentration of 0.4 M to 0.5 M appears to provide a liposome with increased stability as compared with a liposome loaded at 0.60 to 0.65 M. In support of this position, the examiner cites table 1 on pages 22 and 23 of the instant specification. Sample 10 of the instant specification shows loading at 0.60 M sucrose octasulfate and pH 7.25. In this example, there was 24.1 mol% lysophosphatidylcholine after 6 months of storage. In contrast, samples 5 and 7 are drawn to a liposome loaded with 0.45 M sucrose octasulfate and also a pH of 7.25, and these show 7.1% and 7.4% of lyosphosphatidylcholine respectively after 6 months of storage.

As a greater percentage of lysophosphatidylcholine indicates a less stable liposome, the data presented in Table 1 show an increase in stability when the concentration of sulfate groups from sucrose octasulfate is decreased from the prior art amount of 0.65 M to a lower amount of 0.4 M to 0.5 M. This would not have been expected by the skilled artisan, and this also indicates that the concentration of sucrose octasulfate used in loading the liposome is critical to the liposome stability. This showing regarding the criticality of the claimed loading concentration of sucrose octasulfate is evidence of non-obviousness, and applicant's data show that the claimed range of

sucrose octasulfate is critical with regard to the stability of the liposome that is ultimately formed. See MPEP 2144.05(III)(A).

C) Lack of Inherency Regarding Lysophosphatidylcholine After 6 Months: Additionally, the instant claims recite that the composition is stabilized such that after 6 months of storage at the recited conditions, there is less than 20 mol% of lysophosphatidylcholine. The cited prior art references Drummond and Hong do not provide any teachings with regard to the amount of lysophosphatidylcholine after 6 months of storage, and are silent with respect to this issue.

In order to reject such a claim limitation in the absence of an explicit teaching, the examiner must provide rationale or evidence tending to show inherency. See the heading of MPEP 2112(IV). In this case, the evidence appears to tend against inherency. This is because inherency must be based on what is necessarily present in the prior art (e.g. a composition with a pH of 6.5 and between 0.65 M to 1.0 M sulfate groups from sucrose octasulfate), and should not be based on optimization of conditions. See MPEP 2112(IV), first paragraph. In this case, the examiner takes the position that with regard to the composition that is necessarily present in the prior art, this composition would not have been expected to have had the slow rate of degradation such that the percentage of lyso-phosphatidylcholine would have been less than 20% after 6 months of storage.

The prior art examples appear to include a sulfate concentration of between 0.65 M to 1.0 M, as of Hong, paragraph 0104, and a pH of 6.5, as of Hong, end of paragraph 0105. However, the examples in table 1 of the instant specification on pages 20 and 21 of the instant specification that most resemble the prior art examples (e.g. 0.65 M

sucrose octasulfate and pH 6.5) appear to show a greater level of lysophosphatidylcholine after 6 months of storage. The example in the instant specification which appear to be most similar to the prior art are samples 12, 4, and 9, which utilizes a pH of 6.5 and a concentration of sulfate groups of 0.65 M in sample 12 and 0.60 M in samples 4 and 9. These liposomes show that the percentage of lyso-phosphatidylcholine after 6 months is 29.8% in sample 9, 30.2% in sample 4, and 32.7% after 3 months in sample 12. These percentages all exceed the recited maximum of 20% lyso-phosphatidylcholine after the first six months.

As such, the data in the instant specification show that the compositions that are necessarily present in the prior art would have been expected to have degraded to an extent that there would have been more than 20 mol% of lyso-phosphatidylcholine after 6 months of storage. As such, the claimed requirement that there be less than 20 mol% of lyso-phosphatidylcholine after 6 months of storage does not appear to be inherent in the teachings of the prior art.

Non-Statutory 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 1-20 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 24-39 of copending Application No. 15/661,868 (reference application). Although the claims at issue are not identical, they are not patentably distinct from each other because of the following reasons.

Instant claim 1 is drawn to a storage stabilized liposomal irinotecan sucrose octasulfate composition. Said composition is formed in a manner specified by the claims. Said composition is characterized by degrading to less than 20 mol% lyso-phosphatidylcholine after the first six months of storage at 4 degrees Celsius. Said composition has 0.4 to 0.5 M sulfate concentration of sucrose octasulfate and a final pH of 7.0 to 7.5.

Copending claim 1 is drawn to a storage stabilized liposomal irinotecan sucrose octasulfate composition. Said composition is formed in a manner specified by the claims. Said composition is characterized by degrading to less than 20 mol% lyso-phosphatidylcholine after the first six months of storage at 4 degrees Celsius. Said composition has 0.450 to 0.475 M sulfate concentration of sucrose octasulfate and a final pH of 7.25 to 7.50.

The instant and copending claims differ at least because the pH range and sucrose octasulfate concentration range differs between the instant and copending claims. Nevertheless, the subject matter of the copending claims appears to be within the scope of that of the instant claims. This results in a prima facie case of anticipatory-type non-statutory double patnenting.

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

Claims 1-20 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-20 of copending Application No. 15/655,592 (reference application). Although the claims at issue are not identical, they are not patentably distinct from each other because of the following reasons.

Instant claim 1 is drawn to a storage stabilized liposomal irinotecan sucrose octasulfate composition. Said composition is formed in a manner specified by the claims. Said composition is characterized by degrading to less than 20 mol% lyso-phosphatidylcholine after the first six months of storage at 4 degrees Celsius. Said composition has 0.4 to 0.5 M sulfate concentration of sucrose octasulfate and a final pH of 7.0 to 7.5.

Copending claim 1 is drawn to a storage stabilized liposomal irinotecan composition further comprising sucrose octasulfate. Copending claim 4 recites that there is 20 mol% of lyso-phosphatidylcholine after 6 months of storage at 4 degrees Celsius. Copending claims 13 and 14 recite a pH of from 7.0 to 7.5.

The instant and copending claims differ because the copending claims do not recite both the pH and the 20 mol% lysophosphatidylcholine maximum in the same claim. Nevertheless, the skilled artisan would have been motivated to have made a composition that would have degraded a maximum of 20 mol% to lyso-phosphatidylcholine and would have been at a pH of 7.0 to 7.5.

The instant and copending claims differ because the copending claims do not recite the sucrose octasulfate concentration. Nevertheless, the skilled artisan would have been motivated to have optimized the sucrose octasulfate concentration in the copending claims in order to have achieved that concentration recited by the instant claims for predictable administration to a patient and storage stability with a reasonable expectation of success.

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

Conclusion

No claim is allowed at this time.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ISAAC SHOMER whose telephone number is (571)270-7671. The examiner can normally be reached on 7:30 AM to 5:00 PM Monday Through Friday.

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, Frederick F Krass can be reached on (571)272-0580. 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.

ISAAC . SHOMER
Primary Examiner
Art Unit 1612

/ISAAC SHOMER/
Primary Examiner, Art Unit 1612

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Honigman Miller Schwartz and Cohn LLP/Ipsen
350 East Michigan Avenue, Suite 300
Kalamazoo, MI 49007

EXAMINER	
STRONG, TORI	

ART UNIT	PAPER NUMBER
1629	

NOTIFICATION DATE	DELIVERY MODE
12/20/2017	ELECTRONIC

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

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

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

patents@honigman.com
lzerby@honigman.com
arhoades@honigman.com

Office Action Summary	Application No. 15/652,513	Applicant(s) Bayever et al.	
	Examiner TORI STRONG	Art Unit 1629	AIA Status No

-- 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 18 July 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) 1-20 is/are pending in the application.

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

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 1-20 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 15 September 2017 is/are: a)☑ accepted or b)☐ objected to by the Examiner.

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

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

Priority under 35 U.S.C. § 119

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

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

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

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

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

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

Attachment(s)

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

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

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

4) ☐ Other: _____.

DETAILED ACTION

Notice of Pre-AIA or AIA Status

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

Status of Claims

Claims 1-20 are pending in the instant application and are the subject of the Office Action below.

Information Disclosure Statement

The information disclosure statements (IDSs) submitted on July 18, 2017 were filed on the mailing date of the application. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner. Enclosed with this Office Action are return copies of Form PTO/SB/08B with the Examiner's initials and signature indicating those references that have been considered.

Claim Rejections - 35 USC § 103

The following is a quotation of pre-AIA 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, 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.

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 pre-AIA 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.

This application currently names joint inventors. In considering patentability of the claims under pre-AIA 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 pre-AIA 35 U.S.C. 103(c) and potential pre-AIA 35 U.S.C. 102(e), (f) or (g) prior art under pre-AIA 35 U.S.C. 103(a).

Claims 1-5 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Kozuch *et al.* (*The Oncologist*, 2001, 6, pp. 488-495; cited in IDS) and Tsai *et al.* (*Journal of Gastrointestinal Oncology*, 2011, Vol. 2, No. 3, pp. 185-194; cited in IDS) in view of American Cancer Society (ACS)

(http://www.cancer.org/cancer/pancreaticcancer/detailedguide/pancreatic-cancer-what-is-pancreatic-cancer).

Applicant's invention, according to **claim 1**, is directed to a method of treating an exocrine pancreatic cancer comprising administering 60-80 mg/m^2 of irinotecan in a liposome injection formulation having a total volume of 500 mL over about 90 minutes, in combination with a therapeutically effective amount of leucovorin and 5-fluorouracil (5-FU); where the irinotecan liposome injection formulation comprises irinotecan encapsulated within a liposome comprising phosphatidylcholine, cholesterol, and a polyethyleneglycol-derivatized phosphatidyl-ethanolamine, and the irinotecan liposome having a diameter of approximately 80-140 nm. It is important to note that the liposomal irinotecan formulation is also referred to as MM-398 (see specification, *Summary*, p.4, para.7).

Kozuch teaches a method of treating metastatic pancreatic cancer refractory to gemcitabine therapy through administration of a combination called G-FLIP which comprises irinotecan (80 mg/m^2), leucovorin and 5-FU (abs). Kozuch teaches adminsitration of irinotecan, referred to as CPT-11, over 90 minutes (p.490, Fig.1). Kozuch provides a similar composition that comprises irinotecan at 80 mg/m^2 and the other therapeutic agents as instantly claimed for treating pancreatic cancer. Kozuch does not teach irinotecan in liposomal form.

Tsai teaches liposomal therapies for advanced pancreatic cancer to enhance drug delivery. Tsai teaches the liposomal irinotecan has superior efficacy over the free form (p.189, col.1, para.3) and further teaches liposomal irinotecan designated as MM-

398 to have a partial response in pancreatic cancer patients (p.189, col.2, para.2). Tsai further teaches the liposomal irinotecan in combination with 5-FU/LV. Tsai provides teaching that one of ordinary skill in the art would substitute the liposomal form of irinotecan and further combine with the instantly claimed therapeutic agents.

The American Cancer Society (ACS) teaches and defines pancreatic cancer for the general public. The ACS teaches that exocrine tumors are the most common type of pancreatic cancer; where 95% are exocrine cell adenocarcinomas. Therefore treatment that is directed towards pancreatic cancer in general refers to the most common form of exocrine pancreatic cancer.

One of ordinary skill in the art would arrive at the instantly claimed invention having a reasonable expectation of success based on the combined teaching of Kozuch, Tsai and the ACS. Kozuch provides clear teaching of treating pancreatic cancer, of which the ACS discloses exocrine pancreatic cancer is the most common, with the drug combination of irinotecan at 80 mg/m^2 with leucovorin and 5-FU. A skilled artisan would readily gleam from Tsai to interchange irinotecan with the more efficacious MM-398 to combine with leucovorin and 5-FU. The combined art provides rationale for the dosing of irinotecan and the expressed combination with other therapeutic agents for treating pancreatic cancer. Therefore at the time of invention, it was *prima facie* obvious to arrive at the instant claim based on the combined teaching of Kozuch, Tai and the ACS.

Applicant's invention, according to **claims 2-5**, limits claim 1 and requires the described liposomal formulation that is also known as MM-398 to have a dose of 60-80 mg/m^2 of irinotecan and that treatment is refractory to gemcitabine therapy.

As expressed supra, a prima facie case of obviousness is established with the combined teaching of Kozuch, Tsai and the ACS. Kozuch provides teaching of arriving at the dose of irinotecan at 80 mg/m^2, which is within the instantly claimed scope for dosing. Kozuch also teaches treatment refractory to gemcitabine therapy. Tsai provides teaching of the liposomal formulation of irinotecan as MM-398; further teaching its superior benefits over the free form. The instantly claimed limitations fall within the scope of the prior art teaching and therefore as whole remains *prima facie* obvious.

Claims 6-20 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Kozuch *et al.* (*The Oncologist*, 2001, 6, pp. 488-495) and Tsai *et al. (Journal of Gastrointestinal Oncology*, 2011, Vol. 2, No. 3, pp. 185-194) in view of American Cancer Society (ACS) (http://www.cancer.org/cancer/pancreaticcancer/detailedguide/pancreatic-cancer-what-is-pancreatic-cancer), in further view of Yoo *et al.* (*British Journal of Cancer*, 2009, 101, pp. 1658-1663; cited in IDS).

Applicant's invention, according to **claims 6-9**, limits claims 1 and requires leucovorin (l) at 200 mg/m^2 (or racemic at 400 mg/m^2); 5-FU at 2400 mg/m^2; sequential administration beginning on day 1 of a 2 week cycle.

A *prima facie* case of obviousness is established with the combined teaching of Kozuch, Tsai and the ACS for combining liposomal irinotecan with leucovorin and 5-FU. Kozuch teaches treatment of pancreatic cancer through sequential administration of the therapeutic agents where irinotecan, leucovorin and 5-FU is administered in the respective order (p.490, para.1) on day 1 and teaches administration is repeated every 2 weeks (p.488, abs), implicitly a 2-week cycle. However the combined art does not explicitly teach the instantly claimed dosing for leucovorin and 5-FU.

Yoo teaches a method of treating metastatic pancreatic cancer refractory to gemcitabine therapy (abs) through administration of a drug combination regimen called FOIFIRI.3 which comprises irinotecan (70 mg/m^2), leucovorin (400 mg/m^2) and 5-fluorouracil (2000 mg/m^2) (p.1659, col.2, para.3). Yoo teaches administration of 5-FU over a 46 hour period with the entire regimen repeated every 2 weeks. Yoo provides teaching of a similar composition that comprises the same therapeutic agents in similar amounts as instantly claimed.

One of ordinary skill would arrive at the instant limitations having a reasonable expectation of success based on the combine teaching of Kozuch, Tsai, the ACS and Yoo. Kozuch teaches instantly claimed limitations of sequential administration in a 2 week cycle, where Yoo provides for similar dosing in the chemotherapeutic regimen. As skilled artisan would gleam from Yoo, through routine and conventional means, to optimize the range of dosing for treatment; see MPEP 2144.05 (II) for guidance for optimization of ranges. Therefore, the invention as a whole is *prima facie* obvious with the incorporation of the instant limitations.

Applicant's invention, according to **claims 10-19**, is directed to a method of treating an exocrine pancreatic cancer comprising administering 60-80 mg/m^2 of irinotecan in a liposome injection formulation having a total volume of 500 mL over about 90 minutes, in combination with leucovorin (l) at 200 mg/m^2 (or racemic at 400 mg/m^2) and 5-FU at 1800-2400 mg/m^2; where claims 11-15, 18 and 19 disclose limitations that describe MM-398; where claims 16 and 17 require treatment refractory to gemcitabine treatment.

As expressed *supra*, a case of *prima facie* obviousness is established over the instantly claimed limitations. Kozuch and Yoo teaches the drug regimen in similar dosing and Tsai teaches substituting MM-398 for the free form of irinotecan. Kozuch teaches administration over 90 minutes and the ACS teaches that the most common pancreatic cancer is exocrine pancreatic cancer. As explained *supra*, one of ordinary skill would arrive at the instant claims having a reasonable expectation of success and therefore the invention as whole remains *prima facie* obvious.

Applicant's invention, according to **claim 20**, is directed to a method of treating an exocrine pancreatic cancer comprising administering 60-80 mg/m^2 of irinotecan in a liposome injection formulation having a total volume of 500 mL, in combination with leucovorin (l) at 200 mg/m^2 (or racemic at 400 mg/m2) and 5-FU at 2400 mg/m^2; where the claim discloses limitations that describe MM-398; where administration is sequential administration beginning on day 1 of a 2 week cycle.

As expressed *supra*, a case of *prima facie* obviousness is established over the instantly claimed limitations. Kozuch and Yoo teaches the drug regimen in similar

dosing and Tsai teaches substituting MM-398 for the free form of irinotecan. Kozuch teaches sequential administration on day 1 in a 2 week cycle and the ACS teaches that the most common pancreatic cancer is exocrine pancreatic cancer. As explained supra, one of ordinary skill would arrive at the instant claims having a reasonable expectation of success and therefore the invention as whole remains *prima facie* obvious.

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).

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Claims 1-20 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-11, 19-24 and 30-35 of U.S. Patent No. 9,452,162 B2; claims 1-20 and 23-28 of U.S. Patent No. 9,492,442; and claims 1-27 of U.S. Patent No. 9,339,497. Although the claims at issue are not identical, they are not patentably distinct from each other because each of the disclosures set out to claim a method of treating pancreatic cancer refractory to gemcitabine therapy through intravenous administration of irinotecan as the MM-398 liposome, leucovorin as the (l)-form or racemic form and 5-fluorouracil. Each of the disclosures claim the combination in either a similar or identical

dose for the therapeutic agents where the combination is administered in a two week cycle. The claims are obvious variants of each other.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TORI STRONG whose telephone number is (571)272-6333. The examiner can normally be reached on Monday - Friday 8:00 am - 5:00 pm (EST).

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, Jeffrey Lundgren can be reached on (571)272-5541. 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.

TORI STRONG
Examiner
Art Unit 1629

/TORI STRONG/
Examiner, Art Unit 1629

/Kortney L. Klinkel/
Primary Examiner, Art Unit 1611

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/661,868	07/27/2017	Daryl C. Drummond	263266-416012	5763

139696 7590 12/01/2017

Honigman Miller Schwartz and Cohn LLP/Ipsen
350 East Michigan Avenue, Suite 300
Kalamazoo, MI 49007

EXAMINER
SHOMER, ISAAC

ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
12/01/2017	ELECTRONIC

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

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

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

patents@honigman.com
lzerby@honigman.com
arhoades@honigman.com

Office Action Summary	Application No. 15/661,868	Applicant(s) Drummond et al.	
	Examiner ISAAC SHOMER	Art Unit 1612	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 04 October 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) 24-39 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) 24-39 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 _____ 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: _____ .

DETAILED CORRESPONDENCE

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.

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.

Status of Claims

Claims 24-39 are pending and subject to substantive examination.

Claim Interpretation

With regard to claim language, the examiner notes that the claims make use of language in parentheses. The examiner clarifies that the language inside the parentheses are not understood to refer to optional limitations. In contrast, the parentheses are used for the following reasons:

A) To clarify an abbreviation, e.g. SOS for sucrose octasulfate, as of the second line of claim 24.

B) To express a statistical deviance (e.g. as of claim 24, third line).

C) To express a limitation that would result in a sentence that reads in a grammatically unpleasant manner had the parentheses not been used (e.g. the limitation drawn to "(with respect to total phospholipids)" on the fourth and fifth lines of claim 24.

As such, the inclusion of parentheses in claims is not understood to render the claims indefinite.

Cited Art

As relevant art, the examiner cites Drummond et al. (WO 2017/066726 A1). Drummond et al. (hereafter referred to as Drummond '726) is drawn to storage stable liposomal irinotecan compositions. Drummond '726 was published on 20 April 2017. This is later than the earliest effective filing date of the instant application of 21 October 2016. As such, Drummond is not prior art under AIA 35 U.S.C. 102(a)(1).

Drummond '720 has an earliest effective filing date of 16 October 2015, based upon provisional applications to which Drummond '720 claims benefit. This is the same day as the earliest effective filing date of the instant application of 16 October 2015. As such, Drummond '720 is not prior art under AIA 35 U.S.C. 102(a)(2).

Additionally, Drummond '720 has the same inventors as the instant application. As such, despite the earlier filing date, Drummond '720 is not prior art under AIA 35 U.S.C. 102(a)(2) as it does not name another inventor. See MPEP 2154.01(c).

Close Prior Art

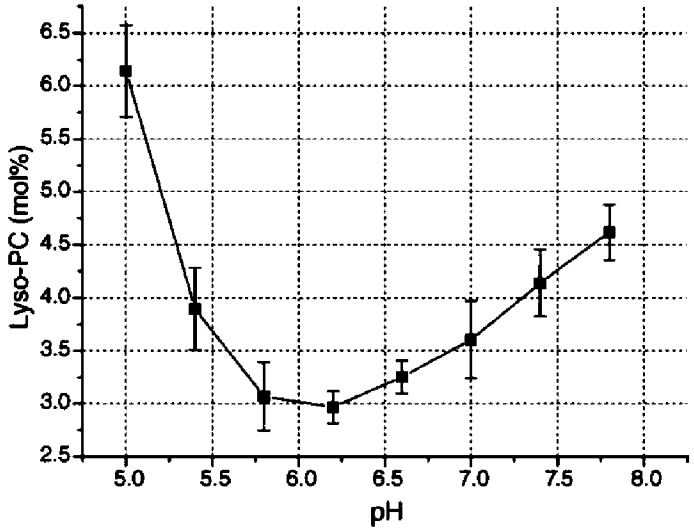
The instant claims are drawn to a liposomal composition comprising irinotecan and sucrose octasulfate. As close and relevant prior art, the examiner cites Drummond et al. (US 2007/0110798 A1) and Hong et al. (US 2007/0116753 A1). The following reasons are provided by the examiner explaining why the instant claims have not been rejected as anticipated by these references or obvious over these references. Also cited by the examiner is Saetern et al. (International Journal of Pharmaceutics, Vol. 288, 2005, pages 73-80).

The examiner notes that the reasons for non-rejection provided here are similar to the reasons provided in the notice of allowance for case 15/331,648 on 10 April 2017 and in case 15/331,318 on 27 April 2017. Both of these cases were abandoned after a notice of allowance for lack of payment of the issue fee.

Liposomes are known to suffer from degradation when in storage. One such form of degradation involves the hydrolysis of phosphatidylcholine, which is a phospholipid molecule with two chains that makes up the structural of the bilayer of the liposome, to lysophosphatidylcholine. Such lysophosphatidylcholine is understood to have poor stability in the liposome bilayer, and a bilayer comprising lysophosphatidylcholine is subject to degradation. The instantly claimed invention is drawn to a liposome that has unexpectedly greater storage stability than the liposomes of the Drummond and Hong prior art references cited above. As such, the instantly claimed invention differs from the composition of the prior art for the following reasons:

A) pH Range: First, the instantly claimed liposome is stored in a medium wherein the pH is 7.25 to 7.50 (as in claim 24) and about 7.3 in claim 35. Hong teaches

that the liposome should be stored at a pH of between 6.0 and 7.5, with a pH of 6.5 as most optimal, as of Hong, paragraph 0115. However, additional relevant prior art shows that storage of a liposome in a pH of about 6.25 to 6.5 has the greatest storage stability, and that deviation from pH 6.25-6.5 results in more degradation during storage as compared to storage at pH 6.5. In support of this position, the examiner cites Saetern et al. (International Journal of Pharmaceutics, Vol. 288, 2005, pages 73-80). Saetern et al. (hereafter referred to as Saetern), teaches the following graph regarding degradation of phosphatidylcholine to lysophosphatidylcholine, as of page 77, right column, Figure 5, which is reproduced below.



As such, the data of Saetern indicates that a pH of about 6.25 provides the greatest stability of a phosphatidylcholine containing liposome. The examiner also notes that the Saetern publication is especially relevant here because Saetern is drawn to encapsulating camptothecin as a drug, and the instant claims are drawn to a liposome that encapsulates irinotecan as a drug, wherein irinotecan is a derivative of camptothecin.

However, in the instant specification, applicant has presented data showing that a pH range of 7.25 to 7.50 unexpectedly provides increased stability as compared to a pH of about 6.5. In support of this position, the examiner cites table 1B on page 26 of the instant specification, which is reproduced below.

Table 1B: *Irinotecan Liposome Stability Ratio and Lyso-PC (after 6 months at 4 °C)*[b]

Sample	Molar (M) concentration of sulfate groups in the sucrosofate entrapped in the liposomes	Stability Ratio	pH	[mol% Lyso-PC] at 6 mos.
1	0.45	1047	6.5	19.5
2	0.475	992	6.5	17
3	0.5	942	6.5	26.5
4	0.6	785	6.5	30.2
5	0.45	1047	7.25	7.1
6	0.45	1047	6.5	14.6
7	0.45	1047	7.25	7.4
8	0.45	1047	7.5	5.4
9	0.6	785	6.5	29.8
10	0.6	785	7.25	24.1
11	0.6	785	7.5	22.8
13	0.45	1047	7.25	9.72

[b] Measured according to Method B, as described herein.

Instant table 1B discloses that a liposome at a pH of 6.5 and a sulfate group concentration of 0.45 M shows 14.6 mol% or 19.5 mol% of lysophosphatidylcholine after 6 months, as of samples #6 and #1 respectively. In contrast, a sample with a pH of 7.25 and an identical sucrose octasulfate concentration of 0.45 M shows only about 7.1 mol% or 7.4 mol% of lyosphosphatidylcholine after 6 months of storage, as of page 21, Table 1, items #5 and #7 respectively. As a greater percentage of lysophosphatidylcholine indicates a less stable liposome, the data presented in Table 1 show an increase in stability when the pH of a sucrose octasulfate containing irinotecan liposome is raised from 6.5 to 7.25.

This increase in stability with increase in pH is at odds with the teachings of the prior art, which indicate that a lower pH of 6.25 to 6.5 is optimal for achieving stability of the liposome. As applicant has shown that the claimed pH range is critical for achieving increased stability, this is understood to be evidence of non-obviousness. See MPEP 2144.05(III)(A).

B) Sucrose Octasulfate Loading Concentration: In the instantly claimed product-by-process, sucrose octasulfate was loaded in a concentration such that the sulfate groups are present in a concentration of 0.4 to 0.5 M, as of part (a) of claim 1. In contrast, in the examples of the prior art, the concentration of sucrose octasulfate inside the liposome was at minimum 0.65 M to about 1.0 M, e.g. as of Hong, page 11, end of paragraph 0104.

Data in the instant application show that loading with a lower level of sucrose octasulfate with a sulfate group concentration of 0.4 M to 0.5 M appears to provide a liposome with increased stability as compared with a liposome loaded at 0.60 to 0.65 M. In support of this position, the examiner cites table 1B of the instant specification, which is reproduced above. Sample 10 of the instant specification shows loading at 0.60 M sucrose octasulfate and pH 7.25. In this example, there was 24.1 mol% lysophosphatidylcholine after 6 months of storage. In contrast, samples 5 and 7 are drawn to a liposome loaded with 0.45 M sucrose octasulfate and also a pH of 7.25, and these show 7.1% and 7.4% of lysophosphatidylcholine respectively after 6 months of storage.

As a greater percentage of lysophosphatidylcholine indicates a less stable liposome, the data presented in Table 1 show an increase in stability when the

concentration of sulfate groups from sucrose octasulfate is decreased from the prior art amount of 0.65 M to a lower amount of 0.4 M to 0.5 M. This would not have been expected by the skilled artisan, and this also indicates that the concentration of sucrose octasulfate used in loading the liposome is critical to the liposome stability. This showing regarding the criticality of the claimed loading concentration of sucrose octasulfate is evidence of non-obviousness, and applicant's data show that the claimed range of sucrose octasulfate is critical with regard to the stability of the liposome that is ultimately formed. See MPEP 2144.05(III)(A).

C) Lack of Inherency Regarding Lysophosphatidylcholine After 6 Months: Additionally, the instant claims recite that the composition is stabilized such that after 6 months of storage at the recited conditions, there is less than 20 mol% of lysophosphatidylcholine. The cited prior art references Drummond and Hong do not provide any teachings with regard to the amount of lysophosphatidylcholine after 6 months of storage, and are silent with respect to this issue.

In order to reject such a claim limitation in the absence of an explicit teaching, the examiner must provide rationale or evidence tending to show inherency. See the heading of MPEP 2112(IV). In this case, the evidence appears to tend against inherency. This is because inherency must be based on what is necessarily present in the prior art (e.g. a composition with a pH of 6.5 and between 0.65 M to 1.0 M sulfate groups from sucrose octasulfate), and should not be based on optimization of conditions. See MPEP 2112(IV), first paragraph. In this case, the examiner takes the position that with regard to the composition that is necessarily present in the prior art, this composition would not have been expected to have had the slow rate of

degradation such that the percentage of lyso-phosphatidylcholine would have been less than 20% after 6 months of storage.

The prior art examples appear to include a sulfate concentration of between 0.65 M to 1.0 M, as of Hong, paragraph 0104, and a pH of 6.5, as of Hong, end of paragraph 0105. However, the examples in table 1 of the instant specification on pages 20 and 21 of the instant specification that most resemble the prior art examples (e.g. 0.65 M sucrose octasulfate and pH 6.5) appear to show a greater level of lysophosphatidylcholine after 6 months of storage. The example in the instant specification which appear to be most similar to the prior art are samples 12, 4, and 9, which utilizes a pH of 6.5 and a concentration of sulfate groups of 0.65 M in sample 12 and 0.60 M in samples 4 and 9. These liposomes show that the percentage of lyso-phosphatidylcholine after 6 months is 29.8% in sample 9, 30.2% in sample 4, and 32.7% after 3 months in sample 12. These percentages all exceed the recited maximum of 20% lyso-phosphatidylcholine after the first six months.

As such, the data in the instant specification show that the compositions that are necessarily present in the prior art would have been expected to have degraded to an extent that there would have been more than 20 mol% of lyso-phosphatidylcholine after 6 months of storage. As such, the claimed requirement that there be less than 20 mol% of lyso-phosphatidylcholine after 6 months of storage does not appear to be inherent in the teachings of the prior art.

Non-Statutory 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).

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Claims 24-39 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-20 of copending Application No. 15/645,645 (reference application). Although the claims at issue are not identical, they are not patentably distinct from each other because of the following reasons:

Instant claim 24 is drawn to a storage stabilized irinotecan sucrose octasulfate liposome. Said liposome is stored at a pH of 7.25 to 7.50 and comprises a concentration of 0.450 to 0.475 M of sulfate concentration in sucrose octasulfate. Said liposome comprises DSPC, cholesterol, and DSPE-mPEG2000. Said composition degrades to 20% or less lyso-phosphatidylcholine after 6 months.

Copending claim 1 is drawn to a storage stabilized irinotecan sucrose octasulfate liposome. Said liposome is stored at a pH of 7 to 7.5 and has a sulfate concentration in sucrose octasulfate of 0.4 to 0.5 M, as of copending claim 1. Said liposome comprises

DSPC, cholesterol, and DSPE-mPEG2000, as of copending claim 2. Said composition degrades to 20% or less lyso-phosphatidylcholine after 6 months.

The instant and copending claims differ because the copending claims recite a broader range of storage pH and sulfate concentration of sucrose octasulfate as compared with the instant claims. Nevertheless, the ranges of the copending claims overlap with those of the instant claims. This results in a prima facie case of obviousness-type non-statutory double patenting.

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

Claims 24-39 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-20 of copending Application No. 15/655,592 (reference application). Although the claims at issue are not identical, they are not patentably distinct from each other because of the following reasons:

Instant claim 24 is drawn to a storage stabilized irinotecan sucrose octasulfate liposome. Said liposome is stored at a pH of 7.25 to 7.50 and comprises a concentration of 0.450 to 0.475 M of sulfate concentration in sucrose octasulfate. Said liposome comprises DSPC, cholesterol, and DSPE-mPEG2000.

Copending claim 1 is drawn to a storage stabilized liposome of irinotecan sucrose octasulfate. Said liposome composition degrades to 20% or less lysophosphatidylcholine after 6 months, as of copending claim 3. Said composition has

a pH of 7.0 to 7.5 or 7.25, as of copending claims 11, 13, and 14. Said liposome composition comprises DSPC, cholesterol, and DSPE-mPEG2000, as of copending claim 5.

The instant and copending claims differ because the copending claims do not recite the required sucrose octasulfate concentration. Nevertheless, as the composition of the copending claims includes sucrose octasulfate, the skilled artisan would have been motivated to have optimized the concentration of sucrose octasulfate in the copending claims in order to have achieved the concentration required by the instant claims.

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

Conclusion

No claim is allowed at this time.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ISAAC SHOMER whose telephone number is (571)270-7671. The examiner can normally be reached on 7:30 AM to 5:00 PM Monday Through Friday.

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, Frederick F Krass can be reached on (571)272-0580. 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.

ISAAC . SHOMER
Primary Examiner
Art Unit 1612

/ISAAC SHOMER/
Primary Examiner, Art Unit 1612

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15/664,930	07/31/2017	Eliel Bayever	263266-416090	2928

139696 7590 12/20/2017

Honigman Miller Schwartz and Cohn LLP/Ipsen
350 East Michigan Avenue, Suite 300
Kalamazoo, MI 49007

EXAMINER	
STRONG, TORI	

ART UNIT	PAPER NUMBER
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patents@honigman.com
lzerby@honigman.com
arhoades@honigman.com

Office Action Summary	Application No. 15/664,930	Applicant(s) Bayever et al.	
	Examiner TORI STRONG	Art Unit 1629	AIA Status Yes

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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 31 July 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) 1-20 is/are pending in the application.

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

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 1-20 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 27 September 2017 is/are: a)☑ accepted or b)☐ objected to by the Examiner.

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

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

Priority under 35 U.S.C. § 119

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

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

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

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

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

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

Attachment(s)

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

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

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

4) ☐ Other: _____.

DETAILED ACTION

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.

Status of Claims

Claims 1-20 are pending in the instant application and are the subject of the Office Action below.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process... may obtain a patent therefor..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the claims that are directed to the same invention so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 1-20 are rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-20 of prior U.S. Patent No. 9,717,724 B2. This is a statutory double patenting rejection.

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 1-20 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-27 of U.S. Patent No. 9,339,497 B2; claims 1-29 of U.S. Patent No. 9,364,473 B2; claims 1-35 of U.S. Patent No. 9,452,162 B2; and claims 1-30 of U.S. Patent No. 9,492,442 B2; and claims 1-24 of U.S. Patent No. 9,717,724 B2. Although the claims at issue are not identical, they are not patentably distinct from each other because each disclosure sets out to claim treatment of pancreatic cancer with the antiproliferative therapeutic regimen that consist of liposomal irinotecan at a dosing of 60, 70 or 80 mg/m^2; leucovorin (*l*-form) at a dose if 200 mg/m^2; and 5-fluorouracil at a dose of 2,400 mg/m^2. Each disclosure teaches and claims treating patients refractory to gemcitabine therapy and treating patients who either are

or not homozygous for the UGT1 A1*28 allele. The closest prior art, as indicated in the record of previous case App. No. 14/812,950 (now patented U.S. Patent No. 9,339,497 B2) is found in Yoo *et al.* (*British Journal of Cancer*, 2009, 101, pp. 1658-163); where Yoo teaches treating pancreatic cancer refractory to gemcitabine therapy with the mFOIRIRI.3 regimen that consists of irinotecan, leucovorin and 5-fluorouracil. However, Yoo requires different dosing and that irinotecan is administered twice where the therapy provides the overall survival for the mFOIRIRI.3 regimen to be 16.6 weeks (or 4.2 months). The instantly claimed invention carves out a specific regimen that requires the dosing of the components and administers the drugs only once within a cycle and further provides for the unexpected result of improving clinical benefit of up to 80% and the increasing the patient population survival of at least 6 months. Therefore the claims are free of the art. However, the claims are obvious variants of the previously patented subject matter and therefore the nonstatutory double patenting rejection is applied.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TORI STRONG whose telephone number is (571)272-6333. The examiner can normally be reached on Monday - Friday 8:00 am - 5:00 pm (EST).

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, Jeffrey Lundgren can be reached on (571)272-5541. 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.

TORI STRONG
Examiner
Art Unit 1629

/TORI STRONG/
Examiner, Art Unit 1629

/Kortney L. Klinkel/
Primary Examiner, Art Unit 1611

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15/664,976	07/31/2017	Keelung Hong	263266-416123	4323

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McNeill Baur PLLC/Ipsen
Ipsen Bioscience, Inc.
125 Cambridge Park Drive
Suite 301
Cambridge, MA 02140

EXAMINER	
SHOMER, ISAAC	

ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
09/11/2018	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):

docketing@mcneillbaur.com
eofficeaction@appcoll.com
patents.us@ipsen.com

Office Action Summary	Application No. 15/664,976	Applicant(s) Hong et al.	
	Examiner ISAAC SHOMER	Art Unit 1612	AIA Status No

-- 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 22 December 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) 160-179 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) 160-179 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 _____ 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: _____.

DETAILED ACTION

Notice of Pre-AIA or AIA Status

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

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.

Claim Rejections - 35 USC § 112(b) – Indefiniteness

The following is a quotation of 35 U.S.C. 112(b):
(b) CONCLUSION.—The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), second paragraph:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 160-171 are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention.

Claim 160 recites “female Albino rats (180-220 g)”. It is unclear if the limitation reciting 180-220 grams is a required limitation or an optional limitation. For the purposes

of examination under prior art, the limitation of 180-220 grams is understood to be optional.

Claim 172 is rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention.

Claim 172 depends upon claim 1. However, claim 1 has been cancelled, so it is unclear as to what is the scope of claim 172. For the purposes of examination under prior art, claim 172 is understood to depend from claim 160.

Non-Statutory 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 160-179 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-35 of U.S. Patent No. 8,147,867.

Although the claims at issue are not identical, they are not patentably distinct from each other because of the following reasons:

The instant claims are drawn to a liposomal composition comprising irinotecan and sucrose octasulfate. Claim 160 recites that a specific percentage of dose is present after 24 and 48 hours. Claim 173 recites that the irinotecan is present as the salt of sucrose octasulfate in a gelated or precipitated state.

Conflicting claim 1 is drawn to a liposome comprising irinotecan and sucrose octasulfate. The liposome has a half-release time of at least 24 hours.

As such, the subject matter of the conflicting claims appears to be within the scope of instant claim 160. As such, the subject matter of the conflicting claims effectively anticipates that of the instant claims, resulting in a prima facie case of anticipatory-type non-statutory double patenting. With regard to instant claim 173, the skilled artisan would have expected that the composition of the conflicting claims would have been in a gelated or precipitated state even if this was not explicitly recited by the conflicting claims.

Claims 160-179 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-17 of U.S. Patent No. 8,329,213.

Although the claims at issue are not identical, they are not patentably distinct from each other because of the following reasons:

The instant claims are drawn to a liposomal composition comprising irinotecan and sucrose octasulfate. Claim 160 recites that a specific percentage of dose is present

after 24 and 48 hours. Claim 173 recites that the irinotecan is present as the salt of sucrose octasulfate in a gelated or precipitated state.

Conflicting claim 1 is drawn to a liposome comprising sucrose octasulfate in the form of a salt of a cationic antineoplastic agent. Conflicting claim 11 recites irinotecan. Conflicting claims 15-16 recite a slow half-release time of between 24-28 hours.

The conflicting claims differ because the recitation of the sucrose octasulfate being in the form of a salt, irinotecan, and the release time are in separate claims. Nevertheless, it would have been prima facie obvious for one of ordinary skill in the art to have combined these features, as they are all recited in the conflicting claims. The combination of these features would have resulted in the subject matter of the instant claims, thereby rendering the instant claims prima facie obvious over the subject matter of the conflicting claims. This results in a prima facie case of obviousness-type non-statutory double patenting.

Claims 160-179 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-17 of U.S. Patent No. 8,703,181. Although the claims at issue are not identical, they are not patentably distinct from each other because of the following reasons:

The instant claims are drawn to a liposomal composition comprising irinotecan and sucrose octasulfate. Claim 160 recites that a specific percentage of dose is present after 24 and 48 hours. Claim 173 recites that the irinotecan is present as the salt of sucrose octasulfate in a gelated or precipitated state.

Conflicting claim 11 is drawn to a method of delivering irinotecan to a tumor comprising delivering a liposomal composition of irinotecan and sucrose octasulfate, wherein the irinotecan and the sucrose octasulfate may be in the form of a salt. Conflicting claims 15-16 are drawn to a slow release time of 24-48 hours.

The instant and conflicting claims differ because the instant claims are composition claims, whereas the conflicting claims are method claims. However, the composition used in the method of the conflicting claims are essentially the same as that recited in the instant claims. As such, the subject matter of the conflicting claims is understood to effectively anticipate that of the instant claims, resulting in a prima facie case of anticipatory-type non-statutory double patenting.

Claims 160-179 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-14 of U.S. Patent No. 8,992,970. Although the claims at issue are not identical, they are not patentably distinct from each other because of the following reasons:

The instant claims are drawn to a liposomal composition comprising irinotecan and sucrose octasulfate. Claim 160 recites that a specific percentage of dose is present after 24 and 48 hours. Claim 168 recites distearoyl phosphatidylcholine (DSPC). Claim 173 recites that the irinotecan is present as the salt of sucrose octasulfate in a gelated or precipitated state.

Conflicting claim 1 is drawn to a liposomal composition comprising irinotecan, sucrose octasulfate, and specific lipids. Conflicting claim 12 recites that the irinotecan

and sucrose octasulfate are in the form of a salt. Conflicting claim 1 also recites distearoyl phosphatidylcholine.

The conflicting claims do not appear to explicitly recite the duration of time that the dose remains in vivo after administration. Nevertheless, the liposomes of the conflicting claims appear to include all of the structural elements of the instant claims. As such, the skilled artisan would have expected that the subject matter of the conflicting claims would have had the long duration in vivo even if this was not explicitly recited by the conflicting claims.

Claims 160-179 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-22 of U.S. Patent No. 8,658,203. Although the claims at issue are not identical, they are not patentably distinct from each other because of the following reasons:

The instant claims are drawn to a liposomal composition comprising irinotecan and sucrose octasulfate. Claim 160 recites that a specific percentage of dose is present after 24 and 48 hours. Claim 173 recites that the irinotecan is present as the salt of sucrose octasulfate in a gelated or precipitated state.

Conflicting claim 1 recites a method of treating a brain tumor comprising administering a liposome comprising irinotecan and sucrose octasulfate, as of conflicting claim 1, parts 1 and 2. Conflicting claims 12-13 recite a half-release time in vivo of 24-28 hours.

The instant conflicting claims differ because the conflicting claims do not explicitly recite that the irinotecan and sucrose form a gelated or precipitated salt. Nevertheless, the skilled artisan would have been aware that irinotecan has a positive charged and sucrose octasulfate has multiple negative charges. As such, the skilled artisan would have understood that the combination of irinotecan with sucrose octasulfate would have predictably formed a salt, which would have been in the gelated or precipitated state, as required by the instant claims with a reasonable expectation of success.

The instant and conflicting claims differ because the conflicting claims are drawn to a method, whereas the instant claims are drawn to a composition. Nevertheless, the composition used in the method of the instant claims appears to be essentially the same as that required by the instantly claimed application. As such, this results in a prima facie case of double patenting.

Claims 160-179 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-19 of U.S. Patent No. 9,717,723. Although the claims at issue are not identical, they are not patentably distinct from each other because of the following reasons:

The instant claims are drawn to a liposomal composition comprising irinotecan and sucrose octasulfate. Claim 160 recites that a specific percentage of dose is present after 24 and 48 hours. Claim 173 recites that the irinotecan is present as the salt of sucrose octasulfate in a gelated or precipitated state.

Conflicting claim 1 is drawn to a method of preparing an irinotecan liposome comprising sucrose octasulfate. The method entails contacting a liposome comprising sucrose octasulfate with irinotecan, as of conflicting claim 1.

The instant and conflicting claims differ because the conflicting claims are method of making claims, whereas the instant claims are composition claims. Nevertheless, the skilled artisan would have understood that the product made by the method of the conflicting claims would have had the structural features required by the instant claims, and as such would have anticipated or rendered prima facie obvious the instantly claimed product. As such, there is a case of non-statutory double patenting despite that the instant claims are composition claims whereas the conflicting claims are method claims.

The instant and conflicting claims also appear to differ because the conflicting claims do not appear to explicitly address the residence time of the liposome in vivo or whether the irinotecan is in the form of a precipitated or gelated salt. This is because, as the composition of made by the method of the conflicting claims, said composition has all of the ingredients recited by the instant specification. As such, the skilled artisan would have expected that such a composition would have expected to have achieved the desired slow release and the desired structure (e.g. a precipitated salt of irinotecan and sucrose octasulfate) with a reasonable expectation of success. This results in an obviousness-type non-statutory double patenting.

Claims 160-179 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-17 of U.S. Patent No. 9,782,349.

Although the claims at issue are not identical, they are not patentably distinct from each other because of the following reasons:

The instant claims are drawn to a liposomal composition comprising irinotecan and sucrose octasulfate. Claim 160 recites that a specific percentage of dose is present after 24 and 48 hours. Claim 173 recites that the irinotecan is present as the salt of sucrose octasulfate in a gelated or precipitated state.

Conflicting claim 1 is drawn to an irinotecan liposome made by a specific process. Claim 1 recites that at least 70% of the irinotecan remains encapsulated after 8 hours in the blood of a mouse. Conflicting claim 4 recites sucrose octasulfate.

The conflicting claims do not appear to recite that the composition is in a gelated or precipitated state, and do not appear to recite an in vivo dose remaining after 24-48 hours that is as long as what is required by the instant claims. Nevertheless, the composition of the conflicting claims, when sucrose octasulfate is the anion, appears to comprise the same ingredients as required by the instant claims. As such, the skilled artisan would have expected the same drug release and form of the composition of the conflicting claims as compared with that of the instant claims. This would have resulted in a prima facie case of obviousness-type non-statutory double patenting.

Claims 160-179 are rejected on the ground of nonstatutory double patenting as being unpatentable over claim 1 of U.S. Patent No. 9,737,528.

Although the claims at issue are not identical, they are not patentably distinct from each other because of the following reasons:

The instant claims are drawn to a liposomal composition comprising irinotecan and sucrose octasulfate. Claim 160 recites that a specific percentage of dose is present after 24 and 48 hours. Claim 173 recites that the irinotecan is present as the salt of sucrose octasulfate in a gelated or precipitated state.

Conflicting claim 1 is drawn to a liposome comprising irinotecan sucrose octasulfate.

Conflicting claim 1 recites "irinotecan hydrochloride" at one point in the claim. While this may appear to preclude the gelated or precipitated state required by instant claim 173, the examiner takes the position that the reference to irinotecan hydrochloride in the claim is understood to be a reference to how the composition of the conflicting claims was prepared. The skilled artisan would have expected that although irinotecan was added as a hydrochloride, it would have gelated or formed a precipitate upon forming a salt with sucrose octasulfate.

Conflicting claim 1 does not appear to provide recitations regarding the amount of dose present at 24 and 48 hours in blood. However, the liposome of the conflicting claims is made from the same material as the liposome of the instant claims. As such, the skilled artisan would have expected that the liposome of the conflicting claims would have remained in blood for the same amount of time as the liposome of the instant claims as it is made from the same materials.

Claims 160-179 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-20 of U.S. Patent No. 9,724,303.

Although the claims at issue are not identical, they are not patentably distinct from each other because of the following reasons:

The instant claims are drawn to a liposomal composition comprising irinotecan and sucrose octasulfate. Claim 160 recites that a specific percentage of dose is present after 24 and 48 hours. Claim 173 recites that the irinotecan is present as the salt of sucrose octasulfate in a gelated or precipitated state.

Conflicting claim 1 is drawn to a liposome comprising irinotecan sucrose octasulfate.

Conflicting claim 1 recites “irinotecan base” at one point in the claim. While this may appear to preclude the gelated or precipitated state required by instant claim 173, the examiner takes the position that the reference to irinotecan base in the claim is understood to be a reference to how the composition of the conflicting claims was prepared. The skilled artisan would have expected that although irinotecan was added as a base, it would have gelated or formed a precipitate upon forming a salt with sucrose octasulfate.

The conflicting claims do not appear to provide recitations regarding the amount of dose present at 24 and 48 hours in blood. However, the liposome of the conflicting claims is made from the same material as the liposome of the instant claims. As such, the skilled artisan would have expected that the liposome of the conflicting claims would have remained in blood for the same amount of time as the liposome of the instant claims as it is made from the same materials.

Claims 160-179 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-20 of U.S. Patent No. 9,730,891.

Although the claims at issue are not identical, they are not patentably distinct from each other because of the following reasons:

The instant claims are drawn to a liposomal composition comprising irinotecan and sucrose octasulfate. Claim 160 recites that a specific percentage of dose is present after 24 and 48 hours. Claim 173 recites that the irinotecan is present as the salt of sucrose octasulfate in a gelated or precipitated state.

Conflicting claim 1 is drawn to a method of using a liposome comprising irinotecan sucrose octasulfate.

Conflicting claim 1 recites "irinotecan base" at one point in the claim. While this may appear to preclude the gelated or precipitated state required by instant claim 173, the examiner takes the position that the reference to irinotecan base in the claim is understood to be a reference to how the composition of the conflicting claims was prepared. The skilled artisan would have expected that although irinotecan was added as a base, it would have gelated or formed a precipitate upon forming a salt with sucrose octasulfate.

The conflicting claims do not appear to provide recitations regarding the amount of dose present at 24 and 48 hours in blood. However, the liposome of the conflicting claims is made from the same material as the liposome of the instant claims. As such, the skilled artisan would have expected that the liposome of the conflicting claims would have remained in blood for the same amount of time as the liposome of the instant claims as it is made from the same materials.

The instant and conflicting claims differ because the instant claims are drawn to a composition, whereas the conflicting claims are drawn to a method. Nevertheless, the skilled artisan would have understood that the composition used in the method of the conflicting claims has the same features as that used in the instant claims. As such, despite this difference, the composition of the instant claims is understood to be prima facie obvious over the recitations of the conflicting claims.

Claims 160-179 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-20 of copending Application No. 15/227,561 (reference application). Although the claims at issue are not identical, they are not patentably distinct from each other because of the following reasons:

The instant claims are drawn to a liposomal composition comprising irinotecan and sucrose octasulfate. Claim 160 recites that a specific percentage of dose is present after 24 and 48 hours. Claim 173 recites that the irinotecan is present as the salt of sucrose octasulfate in a gelated or precipitated state.

Copending claim 1 is drawn to a lipid matrix comprising irinotecan sucrose octasulfate. The term “lipid matrix” is understood to be a liposome.

Copending claim 1 recites “irinotecan base” at one point in the claim. While this may appear to preclude the gelated or precipitated state required by instant claim 173, the examiner takes the position that the reference to irinotecan base in the claim is understood to be a reference to how the composition of the copending claims was

prepared. The skilled artisan would have expected that although irinotecan was added as a base, it would have gelated or formed a precipitate upon forming a salt with sucrose octasulfate.

The copending claims do not appear to provide recitations regarding the amount of dose present at 24 and 48 hours in blood. However, the liposome of the copending claims is made from the same material as the liposome of the instant claims. As such, the skilled artisan would have expected that the liposome of the copending claims would have remained in blood for the same amount of time as the liposome of the instant claims as it is made from the same materials.

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

The examiner notes that even if this rejection were the only rejection pending in regard to this case, it still would not be withdrawn in the absence of a terminal disclaimer or a persuasive argument as to why the rejection is improper. This is because the copending application has the same effective filing date as the instant application, and in such instances, the provisional nonstatutory double patenting rejection should be maintained until the rejection is overcome. See MPEP 804(I)(B)(1)(b)(ii).

Claims 160-179 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-17 and 19 of copending Application No. 15/227,631 (reference application). Although the claims at issue are

not identical, they are not patentably distinct from each other because of the following reasons:

The instant claims are drawn to a liposomal composition comprising irinotecan and sucrose octasulfate. Claim 160 recites that a specific percentage of dose is present after 24 and 48 hours. Claim 173 recites that the irinotecan is present as the salt of sucrose octasulfate in a gelated or precipitated state.

Copending claim 1 is drawn to a lipid matrix comprising irinotecan sucrose octasulfate. The term “lipid matrix” is understood to be a liposome. The claim recites that the lipid matrix comprises irinotecan and sucrose octasulfate which is gelated or precipitated.

The copending claims do not appear to recite a specific amount of time for which the administered dose of irinotecan remains in blood after administration. However, as the composition of the copending claims includes the same ingredients as the composition of the instant claims, the skilled artisan would have expected that the composition of the copending claims would have remained in blood for the same amount of time as required by the instant claims.

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

The examiner notes that even if this rejection were the only rejection pending in regard to this case, it still would not be withdrawn in the absence of a terminal disclaimer or a persuasive argument as to why the rejection is improper. This is because the copending application has the same effective filing date as the instant application, and in such instances, the provisional nonstatutory double patenting

rejection should be maintained until the rejection is overcome. See MPEP 804(I)(B)(1)(b)(ii).

Claims 160-179 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 21-36 of copending Application No. 15/896,389 (reference application). Although the claims at issue are not identical, they are not patentably distinct from each other because of the following reasons:

The instant claims are drawn to a liposomal composition comprising irinotecan and sucrose octasulfate. Claim 160 recites that a specific percentage of dose is present after 24 and 48 hours. Claim 173 recites that the irinotecan is present as the salt of sucrose octasulfate in a gelated or precipitated state.

Copending claim 21 is drawn to a method of delivering irinotecan to a tumor wherein the irinotecan is in a liposome vesicle comprising sucrose octasulfate. Copending claim 25 recites a gelated or precipitated state.

The copending claims do not appear to recite a specific amount of time for which the administered dose of irinotecan remains in blood after administration. However, as the composition of the copending claims includes the same ingredients as the composition of the instant claims, the skilled artisan would have expected that the composition of the copending claims would have remained in blood for the same amount of time as required by the instant claims.

The instant and copending claims differ because the instant claims are composition claims, whereas the copending claims are method claims. However, the skilled artisan would have understood that the composition used in the method of the copending claims would have had the same features as that of the instant claims. As such, the instant claims are effectively anticipated by or prima facie obvious over the composition of the copending claims.

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

The examiner notes that even if this rejection were the only rejection pending in regard to this case, it still would not be withdrawn in the absence of a terminal disclaimer or a persuasive argument as to why the rejection is improper. This is because the copending application has the same effective filing date as the instant application, and in such instances, the provisional nonstatutory double patenting rejection should be maintained until the rejection is overcome. See MPEP 804(I)(B)(1)(b)(ii).

Claims 160-179 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 21-34 of copending Application No. 15/896,436 (reference application). Although the claims at issue are not identical, they are not patentably distinct from each other because of the following reasons:

The instant claims are drawn to a liposomal composition comprising irinotecan and sucrose octasulfate. Claim 160 recites that a specific percentage of dose is present after 24 and 48 hours. Claim 173 recites that the irinotecan is present as the salt of sucrose octasulfate in a gelated or precipitated state.

Copending claim 21 is drawn to a composition comprising a liposomal dispersion of irinotecan and a sulfated sugar, in a gel or precipitate as a salt. Sucrose octasulfate is recited as one option for the sulfated sugar, as of copending claim 21. Copending claim 34 recites that 70% of the irinotecan remains encapsulated 8 hours after injection.

The copending claims do not explicitly recite as to how much of the injected irinotecan remains in vivo after 24 and 48 hours. Nevertheless, as the composition of the copending claims includes all of the structural elements of the instant claims, the skilled artisan would have expected that the composition of the copending claims would have had the same in vivo pharmacokinetic profile as that of the instant claims. This appears to result in the composition of the copending claims effectively anticipating or rendering prima facie obvious that of the instant claims.

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

The examiner notes that even if this rejection were the only rejection pending in regard to this case, it still would not be withdrawn in the absence of a terminal disclaimer or a persuasive argument as to why the rejection is improper. This is because the copending application has the same effective filing date as the instant application, and in such instances, the provisional nonstatutory double patenting

rejection should be maintained until the rejection is overcome. See MPEP 804(I)(B)(1)(b)(ii).

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ISAAC SHOMER whose telephone number is (571)270-7671. The examiner can normally be reached on 7:30 AM to 5:00 PM Monday Through Friday.

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, Frederick F Krass can be reached on (571)272-0580. 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.

ISAAC . SHOMER
Primary Examiner
Art Unit 1612

/ISAAC SHOMER/
Primary Examiner, Art Unit 1612