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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/941,648	09/09/2022	Srinivas G. RAO	ATAI-017/01US 338067-2044	4913

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EXAMINER	
ANDERSON, JAMES D	

ART UNIT	PAPER NUMBER
1629	

NOTIFICATION DATE	DELIVERY MODE
06/15/2023	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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Office Action Summary	Application No. 17/941,648	Applicant(s) RAO et al.	
	Examiner JAMES D ANDERSON	Art Unit 1629	AIA (FITF) 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 12/16/2022.

☐ 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) 1-29 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) 1-29 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: IDS.3P filed 05/04/2023.

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.

Formal Matters

The preliminary amendments to the claims filed 12/16/2022 have been received and entered. Claims 23-29 were newly added. Claims 1-29 are pending and under examination.

Priority

This application claims benefit of priority to U.S. Provisional Application No. 63/242,926, filed 09/10/2021.

Information Disclosure Statement

Applicant's Information Disclosure Statements filed 02/07/2023 and 06/08/2023 have been received and entered into the present application. As reflected by the attached, completed copies of form PTO-1449, the Examiner has considered the cited references to the extent that they comply with the provisions of 37 C.F.R. §1.97, §1.98 and MPEP §609.

Lined-through references fail to comply with the provisions of 37 C.F.R. §1.97, §1.98 and MPEP §609 because they do not satisfy the stipulations of 37 C.F.R. 1.98(a) and/or §1.98(b) regarding the citation of non-patent literature. 37 C.F.R. 1.98(a) requires a legible copy of for each cited pending unpublished U.S. application, the application specification including the claims, and any drawing of the application, or that portion of the application which caused it to

be listed including any claims directed to that portion. C.F.R. §1.98(b) explicitly states each U.S. application listed in an information disclosure statement must be identified by the inventor, application number, and filing date.

Applicant's cited non-patent literature reference 034 in the IDS filed 02/07/2023 has been lined-through for failing to provide the relevant information required by 37 C.F.R. §1.98(b)(3), which requires that each U.S. application listed in an information disclosure statement **must be identified by the inventor**, application number, and filing date.

Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 C.F.R. §1.97(e). MPEP §609.05(a).

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Third-Party Submission Under 37 CFR 1.290

Receipt is acknowledged of the third-party submission under 37 CFR 1.290 filed 05/04/2023. The references cited therein have been considered by the Examiner.

Claim Rejections - 35 USC § 112 – 2nd Paragraph

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.

"The primary purpose of this requirement of definiteness of claim language is to ensure that the scope of the claims is clear so the public is informed of the boundaries of what constitutes infringement of the patent. A secondary purpose is to provide a clear measure of what applicants regard as the invention so that it can be determined whether the claimed invention meets all the criteria for patentability and whether the specification meets the criteria of 35 U.S.C. 112, first paragraph with respect to the claimed invention.", (see MPEP § 2173).

Claims 1, 6-21, and 22-27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Independent claim 1 recites a method of increasing and prolonging exposure to ibogaine in a patient, while reducing exposure to noribogaine and associated risk of QT prolongation

comprising administering to the patient: (a) a drug that inhibits the metabolism of ibogaine; and (b) an effective amount of ibogaine, or a pharmaceutically acceptable salt thereof.

Independent claim 22 recites a method of increasing the bioavailability of ibogaine in a patient in need thereof, comprising administering to the patient: (a) a drug that inhibits the metabolism of ibogaine; and (b) an effective amount of ibogaine, or a pharmaceutically acceptable salt thereof.

A person of ordinary skill in the art would not be reasonable apprised of the metes and bounds of the claimed "effective amount of ibogaine" because the claims are not drawn to a therapeutic treatment of any disease or disorder, but rather to decreasing the metabolism of ibogaine such that exposure and bioavailability to ibogaine is increased. As such, it is unclear for what the claimed "effective amount of ibogaine" is effective for.

Dependent claims 26-27, for example, recite that the effective of ibogaine administered is "lower" than an effective amount of ibogaine without administration of the drug that inhibits metabolism of ibogaine. Without knowing what the "effective amount of ibogaine" is effective for, a person of ordinary skill in the art would have no way of ascertaining whether any given "effective amount" is lower than any other "effective amount".

As evidence that widely varying amounts of ibogaine have been administered to patients for different purposes, the Examiner cites **MASH *ET AL.*** (Annals of the New York Academy of Sciences, 2006, 914: 394-401) (Newly Cited) and **GLUE *ET AL.*** (The Journal of Pharmacology, 2015, 20 pages (First Published February 4, 2015) (Cited by Applicants in IDS filed 02/07/2023). Mash et al. administered 500 mg, 600 mg, or 800 mg ibogaine HCl to human subjects as a potential treatment for drug dependence (paragraph bridging p.395-396). Glue et al. administered a single oral dose of 20 mg ibogaine to healthy human subjects. Also see

dependent claim 28, where Applicants disclose the "effective amount" of ibogaine is about 20 mg to about 1000 mg.

Because dependent claims require "the effective amount" of ibogaine to be lower than "an effective amount" of ibogaine without administration of the drug that inhibits metabolism of ibogaine, even the 20 mg dose administered in Glue et al., which is "an effective amount of ibogaine" as evidenced by dependent claim 28, is also an effective amount that is about 5% to about 50% lower than some other "effective amount" between about 20 mg and about 1000 mg, *e.g.*, 40 mg.

Claim 25 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 25 depends from claim 24, which depends from claim 1. Claim 1 sets forth two primary elements, namely, administering a patient: (a) a drug that inhibits the metabolism of ibogaine; and (b) an effective amount of ibogaine, or a pharmaceutically acceptable salt thereof. Claim 25 recites that the patient's ibogaine C_{max} is increased by about 5% to about 30% compared to a patient administered the effective amount of ibogaine without administration of the drug that inhibits the metabolism of ibogaine (i.e., functional descriptive language). However, this later dependent limitation is indefinite because it is not clear from either the Specification or common teachings in the art how this limitation is intended to further limit the claims. For example, it is not clear if this limitation is limiting to the effective amount of ibogaine administered, the drug that inhibits the metabolism of ibogaine, the dose of the drug that inhibits the metabolism of ibogaine, the timing of the administration of the ibogaine in

relation to the administration of the drug that inhibits the metabolism of ibogaine, or something else entirely.

The Specification does not teach or provide a nexus between the degree of increase in ibogaine C_{max} that Applicants claim to achieve by their method with any particular component of the method or the manner in which it is carried out. Applicants do not, for example, provide any working example demonstrating that a patient's ibogaine C_{max} is increased by about 5% to about 30% compared to a patient administered the effective amount of ibogaine without administration of the drug that inhibits the metabolism of ibogaine. In contrast, **GLUE *ET AL.*** (The Journal of Pharmacology, 2015, 20 pages (First Published February 4, 2015) (Cited by Applicants in IDS filed 02/07/2023) teach that pretreating human subjects for 6 days with the CYP2D6 inhibitor paroxetine prior to administering a single oral 20 mg dose of ibogaine to the subjects **increases the subject's C_{max} by over 96%** (29.5 ng/mL in subjects pre-treated with paroxetine vs. 1.1 ng/mL in subjects without administration of paroxetine).

A person of ordinary skill in the art would not be reasonably apprised what "effective amount" of ibogaine administered with what drug that inhibits the metabolism of ibogaine in what dose of the drug that inhibits the metabolism of ibogaine and in what administration regimen would elicit the claimed ibogaine C_{max} increase by about 5% to about 30% compared to a patient administered the effective amount of ibogaine without administration of the drug that inhibits the metabolism of ibogaine.

Claim Rejections - 35 USC § 112, 1st Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112(a):

> (a) IN GENERAL.—The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to

> make and use the same, and shall set forth the best mode contemplated by the inventor or joint inventor of carrying out the invention.

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

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5 and 17-29 are rejected under 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor or a joint inventor, or for applications subject to pre-AIA 35 U.S.C. 112, the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims require administration of "a drug that inhibits the metabolism of ibogaine". See Claims 1-2 and 22.

The Specification discloses that ibogaine is rapidly metabolized by CYP2D6 in the gut wall and liver to its primary metabolite, noribogaine, citing Koenig and Hilber (2015) (Specification at [0003]). The Specification describes CYP2D6 inhibitors as drugs that inhibit the metabolism of ibogaine (Specification at [0008]).

The Specification does not describe any other drugs that inhibit the metabolism of ibogaine and a person of ordinary skill in the art would not be able to predict the operability of any given drug to do so. What Applicants describe is one sub-genus, i.e., CYP2D6 inhibitors, that have the disclosed and claimed effect of inhibiting the metabolism of ibogaine.

Applicants were clearly not in possession of the claimed methods of administering "a drug that inhibits the metabolism of ibogaine", other than administering CYP2D6 inhibitors.

Rather, the disclosure merely directs those skilled in the art to figure out, through random hit-or-miss testing, what drugs out of all drugs that exist in the art are capable of inhibiting the metabolism of ibogaine.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, states that Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention, for purposes of the written description inquiry, is whatever is now claimed (see page 1117). The court in *Eli Lilly* held that an adequate written description of a claimed genus requires more than a generic statement of an invention's boundaries. *Regents of the University of California v. Eli Lilly & Co.*, 119 F3d at 1568. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. *Regents of the University of California v. Eli Lilly & Co.*, 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

Here, Applicants have failed to provide sufficient distinguishing characteristics of drugs that inhibit the metabolism of ibogaine. Indeed, they describe such drugs only by a single functional characteristic (CYP2D6 inhibitors).

A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or structural features common to the members of the genus, which features constitute a substantial portion of the genus, so that one of skill in the art can "visualize or recognize" the members of the genus (Emphasis added). *Regents*

of the University of California v. Eli Lilly & Co., 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

Here too, the species disclosed by Applicants, which are all inhibitors of CYP2D6, are not representative of the claimed genus of "a drug that inhibits the metabolism of ibogaine".

As the courts have repeatedly stated, the purpose of the written description requirement is to "ensure that the scope of the right to exclude, as set forth in the claims, does not overreach the scope of the inventor's contribution to the field of art as described in the patent specification." *Rochester*, 358 F.3d at 920 (quoting *Reiffin v. Microsoft Corp.*, 214 F.3d 1342, 1345 [54 USPQ2d 1915] (Fed. Cir. 2000)).

Here, Applicants desire patent protection for administering any "drug that inhibits the metabolism of ibogaine" in combination with administration of ibogaine to patients. To support such broad protection and right to exclude, Applicants describe the claimed genus only by describing CYP2D6 inhibitors, which were already known in the art to inhibit metabolism of ibogaine.

The Examiner acknowledges that a working example or exemplified embodiment is not necessarily a requirement for description. However, where a generic claim term is present in a claim, the specification must convey enough information, e.g., via sufficient representative examples, to indicate invention of species sufficient to constitute the genus. *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 323 F.3d 956, 967 2 (Fed. Cir. 2002). The written description requirement "requires a description of an invention, not an indication of a result that one might achieve if one made that invention." *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997); see also *Novozymes A/S v. DuPont Nutrition Biosciences APS*, 723 F.3d 1336, 1350 (Fed. Cir. 2013) ("A patent…'is not a reward for the search, but compensation for its

successful conclusion.' … For that reason, the written description requirement prohibits a patentee from 'leaving it to the … industry to complete an unfinished invention.' " (citations omitted)).

At best, Applicant' s Specification directs those skilled in the art to figure out, through random hit-or-miss testing, what drugs out of all drugs that exist in the art are capable of inhibiting the metabolism of ibogaine. This activity would require "excessive trial and error experimentation" (FF 14). See *In re '318 Patent Infringement Litigation*, 583 F.3d 1317, 1327 (Fed. Cir. 2009) ("[A]t the end of the day, the specification, even read in light of the knowledge of those skilled in the art, does no more than state a hypothesis and propose testing to determine the accuracy of that hypothesis. That is not sufficient.").

Accordingly, the specification does not provide adequate written description of the claimed genus of "a drug that inhibits the metabolism of ibogaine". One of skill in the art would not recognize from the disclosure that the applicant was in possession of the genus. The specification does not clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed (see Vas-Cath at page 1116).

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1115).

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.
>
> (a)(2) the claimed invention was described in a patent issued under section 151, or in an application for patent published or deemed published under section 122(b), in which the patent or application, as the case may be, names another inventor and was effectively filed before the effective filing date of the claimed invention.

Claim(s) 1, 6-7, 13-15, 17-24, and 26-29 is/are rejected under 35 U.S.C. 102(a)(1) as being anticipated by **GLUE *ET AL.*** (The Journal of Pharmacology, 2015, 20 pages (First Published February 4, 2015) (Cited by Applicants in IDS filed 02/07/2023).

GLUE ET AL. teach pretreating human subjects for 6 days with the CYP2D6 inhibitor paroxetine prior to administering a single oral 20 mg dose of ibogaine to the subjects (Abstract), thus anticipating claims 1, 6-7, 13-15, 17-19, 22, and 28-29. They teach the C_{max} of noribogaine was 12.7 ng/mL in subjects pre-treated with paroxetine and 18.7 ng/mL in subjects without administration of paroxetine, a reduction of about 32% (Placebo) (Table 1), thus anticipating claims 20-21 and 23. They teach the C_{max} of ibogaine was 29.5 ng/mL in subjects pre-treated with paroxetine and 1.1 ng/mL in subjects without administration of paroxetine (Placebo) (Table 1), thus anticipating claim 24.

Regarding Claims 26-27, Applicants disclose (and claim) that the "effective amount" of ibogaine is about 20 mg to about 1000 mg. See, for example, dependent Claim 28. As such, administration of 20 mg ibogaine is inherently about 5% to about 50% lower than an "effective amount" of ibogaine without administration of the drug that inhibits the metabolism of ibogaine.

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.

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

Claims 1-7 and 10-29 rejected under 35 U.S.C. 103(a) as being unpatentable over **US 2003/0144220 A1** (Published July 31, 2003) (Cited by Applicants in IDS filed 02/07/2023) and **GLUE *ET AL.*** (The Journal of Pharmacology, 2015, 20 pages (First Published February 4, 2015) (Cited by Applicants in IDS filed 02/07/2023) in view of **MASH *ET AL.*** (Frontiers in Pharmacology, June 2018, vol. 9, article 529, 12 pages) (Cited by Applicants in IDS filed

02/07/2023) and **KOENIG *ET AL.*** (Molecules, 2015, vol. 20, pages 2208-2228) (Cited by Applicants in IDS filed 02/07/2023).

US '220 teaches the use of a CYP2D6 inhibitor in combination with a drug having CYP2D6 catalyzed metabolism in order to improve the drug's pharmacokinetic profile (Abstract; Claim 1). See also [0018] ("…a method of administering a drug for which the major clearance mechanism in humans is CYP2D6 mediated oxidative biotransformation…or a pharmaceutically acceptable salt thereof, in combination with a CYP2D6 inhibitor, or a pharmaceutically acceptable salt thereof, to a human in need of the intended pharmaceutical activity of such drug…"). It teaches examples of drugs for which the major clearance mechanism in humans is CYP2D6 mediated oxidative biotransformation include, *inter alia*, ibogaine ([0028]; Claim 9). It teaches the CYP2D6 inhibitor is, inter alia, quinidine as recited in claims 7 and 10 ([0030]; Claim 11).

GLUE *ET AL.* teach pretreating human subjects for 6 days with the CYP2D6 inhibitor paroxetine prior to administering a single oral 20 mg dose of ibogaine to the subjects (Abstract), thus anticipating claims 1, 6-7, 13-15, 17-19, 22, and 26-29. They teach the C_{max} of noribogaine was 12.7 ng/mL in subjects pre-treated with paroxetine and 18.7 ng/mL in subjects without administration of paroxetine, a reduction of about 32% (Placebo) (Table 1), thus anticipating claims 20-21 and 23. They teach the C_{max} of ibogaine was 29.5 ng/mL in subjects pre-treated with paroxetine and 1.1 ng/mL in subjects without administration of paroxetine (Placebo) (Table 1), thus anticipating claim 24.

US '220 and Glue et al. differ from Claims 2-5 in so far as they do not disclose administering ibogaine and an inhibitor of ibogaine metabolism to treat a condition that is treatable with ibogaine, e.g., substance abuse disorder or opioid use disorder.

MASH *ET AL.* teach ibogaine may be effective for transitioning opioid and cocaine dependent individuals to sobriety (Abstract). They teach administering oral doses of ibogaine HCl (8-12 mg/kg) in gel caps to patients with opioid or cocaine dependence (paragraph bridging p.2-3). They teach that ibogaine therapy administered in a safe dose range diminishes opioid withdrawal symptoms and reduces drug cravings. They teach that their results support product development of single oral dose administration of ibogaine for the treatment of opioid withdrawal during medically supervised detoxification to transition drug dependent individuals to abstinence (Abstract). They teach ibogaine decreased drug craving and improved depressive symptoms when administered in a range of 500–1000 mg and that this dosage range appears to be a safe and effective treatment for interrupting the opioid addiction syndrome (p.8, left column).

KOENIG ET AL. teach ibogaine is anti-addictive in humans as the drug alleviates drug craving and impedes relapse of drug use (Abstract; p.2209, 2nd Paragraph). They teach ibogaine is metabolized to its main metabolite noribogaine in the gut wall and liver primarily by cytochrome P4502D6 (CYP2D6) enzymes (p.2212, 2nd Paragraph). They teach that ibogaine intake is typically not immediately accompanied by deleterious adverse events and considering that ibogaine has a half-life of only 4-7 hours in human plasma, the appearance of fatalities 24-76 hours after drug ingestion can hardly be attributed to the sole action of the alkaloid [ibogaine] (p.2219, 2nd full paragraph). They also teach QT interval prolongation after ibogaine administration typically lasts for more than 24 hours and has been observed to sometimes persist for longer than a week (*Id.*). They conclude that it seems plausible that ibogaine's long-lived metabolite noribogaine, rather than the parent drug itself, constitutes the major cardiac risk after ibogaine intake (*Id.*).

It would have been obvious to a person of ordinary skill in the art to administer a drug that inhibits the metabolism of ibogaine, e.g., an inhibitor of CYP2D6, and an effective amount of ibogaine to a patient with the predictable result that the bioavailability and exposure to ibogaine in the patient would be increased and exposure to its metabolite noribogaine would be reduced. An example rationale that supports the Examiner's conclusion of obviousness is the explicit teachings of the cited prior that not only expressly suggest Applicant's claimed methods (US '220) but also had already carried out Applicant's claimed methods (Glue et al.).

As discussed above (see 35 U.S.C. 102(a)(1) rejection), Glue et al. anticipates claims 1, 6-7, 13-15, 17-24, and 28-29, which is the epitome of obviousness - "lack of novelty is the epitome of obviousness" (May, 574 F.2d at 1089, 197 USPQ at 607 (citing *In re Pearson*, 494 F.2d 1399, 1402, 181 USPQ 641, 644 (CCPA 1974)).

Regarding claims 2-5, it would be obvious to administer the 20 mg dose of ibogaine in combination with administration of the CYP2D6 inhibitor paroxetine taught in Glue et al. to patients with substance abuse disorder or opioid use disorder because this is precisely what ibogaine has been used in the art to treat as evidenced by Mash et al. and Koenig et al.

Regarding claim 10, US '220 teaches that quinidine is a CYP2D6 inhibitor useful for administering in combination with a drug for which the major clearance mechanism in humans is CYP2D6 mediated oxidative biotransformation such as ibogaine. A person of ordinary skill in the art would reasonably expect any known inhibitor of CYP2D6 to have similar activity to paroxetine taught in Glue et al. in increasing the exposure and bioavailability of ibogaine and reducing exposure to its metabolite noribogaine.

Regarding claims 11-12 and 16, Glue et al. teach pretreating human subjects for 6 days with the CYP2D6 inhibitor paroxetine prior to administering a single oral 20 mg dose of

ibogaine to the subjects. They teach paroxetine was administered between days 2-15 and on day 8 a single oral dose of ibogaine was administered to all subjects. *In re Burhans*, 154 F.2d 690, 69 USPQ 330 (CCPA 1946) (selection of any order of performing process steps is prima facie obvious in the absence of new or unexpected results). Also, "[w]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). Here, the combined teachings of the cited prior art disclose the general conditions for administering ibogaine and an inhibitor of ibogaine metabolism such as a CYP2D6 inhibitor to patients. Administering the CYP2D6 days before, within 12 hours before, or "with" ibogaine would all have been prima facie obvious to a person of ordinary skill in the art and reasonably expected to increase the exposure and bioavailability of ibogaine and reduce exposure to its metabolite noribogaine.

Claim 25 depends from claim 24, which depends from claim 1 and requires that the patient's ibogaine C_{max} is increased by about 5% to about 30% compared to a patient administered the effective amount of ibogaine without administration of the drug that inhibits the metabolism of ibogaine. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). Here, the combined teachings of the cited prior art describe the general conditions for increasing ibogaine C_{max} in a patient by administration of a drug that inhibits the metabolism of ibogaine, e.g., paroxetine. A person of ordinary skill in the art would have a reasonable expectation of success in adjusting the degree of increase in ibogaine C_{max} by adjusting the dose and/or administration regimen of the drug that inhibits the metabolism of ibogaine. For example, the art teaches that administering 10 mg

paroxetine on days 2-3 and 20 mg paroxetine on days 4-15 with administration of a single oral dose of 20 mg ibogaine on Day 8 increases the subject's C_{max} by over 96% (29.5 ng/mL in subjects pre-treated with paroxetine vs. 1.1 ng/mL in subjects without administration of paroxetine). A person of ordinary skill in the art would reasonably expect that, for example, administration of a single oral dose of 5 mg paroxetine on the same day as administration of 20 mg ibogaine would increase the Cmax of ibogaine by a smaller amount.

Claim(s) 8 is/are rejected under 35 U.S.C. 103 as being unpatentable over **US 2003/0144220 A1** (Published July 31, 2003) and **GLUE *ET AL.*** (The Journal of Pharmacology, 2015, 20 pages (First Published February 4, 2015) in view of **MASH *ET AL.*** (Frontiers in Pharmacology, June 2018, vol. 9, article 529, 12 pages) and **KOENIG *ET AL.*** (Molecules, 2015, vol. 20, pages 2208-2228) as applied to claims 1-7 and 10-29 above, and further in view of **DASH *ET AL.*** (Xenobiotica, 2018, vol. 48, no. 9, pages 945-957) (Newly Cited).

The teachings of US '220, Glue et al., Mash et al., and Koenig et al. are as applied to claims 1-7 and 10-29 supra, which teachings are herein incorporated by reference in their entirely and applied equally to claim 8.

Claim 8 requires that the CYP2D6 inhibitor is bupropion.

DASH ET AL. teach bupropion increased the systemic exposure of nebivolol (CYP2D6 substrate) by seven times and its metabolite 4-hydroxy nebivolol by three times due to its CYP2D6 inhibition potential. They teach numerous CYP2D6 substrate drugs whose exposure and bioavailability are increased when administered with bupropion (p.952, right column, "Bupropion as perpetrator drug").

The Examiner's analysis and determination of obviousness as applied to claims 1-7 and 10-29 supra is herein incorporated by reference and applied equally to claim 8. With specific regard to claim 8, it would have been obvious to a person of ordinary skill in the art to administer any known CYP2D6 inhibitor to a patient being administered ibogaine, including bupropion as recited in claim 8, with the expectation that it will increase exposure and bioavailability of ibogaine and decrease exposure to its metabolite norbogaine. Clearly, both paroxetine and bupropion predictably inhibit metabolism of drugs metabolized by CYP2D6 as evidenced by both Glue et al. and Dash et al.

Claim(s) 9 is/are rejected under 35 U.S.C. 103 as being unpatentable over **US 2003/0144220 A1** (Published July 31, 2003) and **GLUE *ET AL.*** (The Journal of Pharmacology, 2015, 20 pages (First Published February 4, 2015) in view of **MASH *ET AL.*** (Frontiers in Pharmacology, June 2018, vol. 9, article 529, 12 pages) and **KOENIG *ET AL.*** (Molecules, 2015, vol. 20, pages 2208-2228) as applied to claims 1-7 and 10-29 above, and further in view of **JEPPESEN *ET AL.*** (Eur. J. Clin. Pharmacol., 1996, vol. 51, pages 73-78) (Cited by Applicants in IDS filed 02/07/2023).

The teachings of US '220, Glue et al., Mash et al., and Koenig et al. are as applied to claims 1-7 and 10-29 supra, which teachings are herein incorporated by reference in their entirely and applied equally to claim 9.

Claim 9 requires that the CYP2D6 inhibitor is fluoxetine.

Jeppesen et al. teach administering a single oral dose of, inter alia, fluoxetine or paroxetine, to healthy men followed 3 hours later by sparteine, a CYP2D6 substrate (Abstract). They teach that with increasing doses, there was a statistically significant increase in the

sparteine metabolic ratio for all four administered SSRIs, including fluoxetine and paroxetine (Abstract; Fig. 1). They teach that the investigation confirms that paroxetine and fluoxetine are potent inhibitors of CYP2D6 (Abstract).

The Examiner's analysis and determination of obviousness as applied to claims 1-7 and 10-29 supra is herein incorporated by reference and applied equally to claim 9. With specific regard to claim 9, it would have been obvious to a person of ordinary skill in the art to administer any known CYP2D6 inhibitor to a patient being administered ibogaine, including fluoxetine as recited in claim 9, with the expectation that it will increase exposure and bioavailability of ibogaine and decrease exposure to its metabolite norbogaine. Clearly, both paroxetine and fluoxetine predictably inhibit metabolism of drugs metabolized by CYP2D6 as evidenced by both Glue et al. and Jeppesen et al.

Conclusion

Applicant is requested to specifically point out the support for any amendments made to the disclosure in response to this Office action, including the claims (M.P.E.P. §§ 714.02 and 2163.06). In doing so, applicant is requested to refer to pages and line (or paragraph) numbers (if available) in the as-filed specification, not the published application. Due to the procedure outlined in M.P.E.P. § 2163.06 for interpreting claims, other art may be applicable under 35 U.S.C. § 102 or 35 U.S.C. § 103(a) once the aforementioned issue(s) is/are addressed.

Applicant is reminded that MPEP §2001.06(b) clearly states that "[t]he individuals covered by 37 C.F.R. 1.56 have a duty to bring to the attention of the examiner, or other Office official involved with the examination of a particular application, information within their knowledge as to other copending United States applications which are "material to patentability"

of the application in question." See *Armour & Co. v. Swift & Co.*, 466 F.2d 767, 779, 175 USPQ 70, 79 (7th Cir. 1972). MPEP §2001.06(b) clearly indicates that "if a particular inventor has different applications pending in which similar subject matter but patentably indistinct claims are present that fact must be disclosed to the examiner of each of the involved applications." See *Dayco Prod. Inc. v. Total Containment, Inc.*, 329 F.3d 1358, 1365-69, 66 USPQ2d 1801, 1806-08 (Fed. Cir. 2003).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JAMES D ANDERSON whose telephone number is (571)272-9038. The examiner can normally be reached on Monday-Friday, 8:30 am - 5:00 pm.

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.

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