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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
90/019,779	12/16/2024	7919499	113331.0000030	8002

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EXAMINER
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ART UNIT	PAPER NUMBER
3991	

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04/30/2025	PAPER

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.

ALKERMES EXHIBIT 2006
Apotex Inc. v. Alkermes Pharma Ireland Limited
IPR2025-00514

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EX PARTE REEXAMINATION COMMUNICATION TRANSMITTAL FORM

REEXAMINATION CONTROL NO. *90/019,779* .

PATENT UNDER REEXAMINATION *7919499* .

ART UNIT *3991* .

Enclosed is a copy of the latest communication from the United States Patent and Trademark Office in the above identified *ex parte* reexamination proceeding (37 CFR 1.550(f)).

Where this copy is supplied after the reply by requester, 37 CFR 1.535, or the time for filing a reply has passed, no submission on behalf of the *ex parte* reexamination requester will be acknowledged or considered (37 CFR 1.550(g)).

Office Action in Ex Parte Reexamination	Control No. 90/019,779	Patent Under Reexamination 7919499	
	Examiner LORA E DRISCOLL	Art Unit 3991	AIA (First Inventor to File) Status No

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

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

b. ☐ This action is made FINAL.

c. ☑ A statement under 37 CFR 1.530 has not been received from the patent owner.

A shortened statutory period for response to this action is set to expire 2 month(s) from the mailing date of this letter. Failure to respond within the period for response will result in termination of the proceeding and issuance of an *ex parte* reexamination certificate in accordance with this action. 37 CFR 1.550(d). **EXTENSIONS OF TIME ARE GOVERNED BY 37 CFR 1.550(c).** If the period for response specified above is less than thirty (30) days, a response within the statutory minimum of thirty (30) days will be considered timely.

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☐ Information Disclosure Statement, PTO/SB/08.
3. ☐ Interview Summary, PTO-474.
4. ☐ _____.

Part II SUMMARY OF ACTION

1a. ☑ Claims 1-13 are subject to reexamination.
1b. ☐ Claims _____ are not subject to reexamination.
2. ☐ Claims _____ have been canceled in the present reexamination proceeding.
3. ☐ Claims _____ are patentable and/or confirmed.
4. ☑ Claims 1-13 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ The drawings, filed on _____ are acceptable.
7. ☐ The proposed drawing correction, filed on _____ has been (7a) ☐ approved (7b) ☐ disapproved.
8. ☐ Acknowledgment is made of the priority claim under 35 U.S.C. 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the certified copies have
   1 ☐ been received.
   2 ☐ not been received.
   3 ☐ been filed in Application No. _____.
   4 ☐ been filed in reexamination Control No. _____.
   5 ☐ been received by the International Bureau in PCT application No. _____.
   * See the attached detailed Office action for a list of the certified copies not received.
9. ☐ Since the proceeding appears to be in condition for issuance of an *ex parte* reexamination certificate 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.
10. ☐ Other: _____

cc: Requester (if third party requester)

Notice of Pre-AIA or AIA Status

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

Reexamination—Non-Final Action

Procedural Posture

A third-party requester filed a request for *ex parte* reexamination of claims 1-13 of US Patent 7,419,499. Reexamination was ordered on 1/28/25.

The Challenged Patent Claims

Claims 1-13 of US Patent 7,419,499 are under reexamination in this proceeding. Claim 1 is independent and representative:

> A method for treating an individual in need of naltrexone comprising the step of parenterally administering a long acting formulation comprising about 310 mg to about 480 mg of naltrexone and a biocompatible polymer to the individual wherein the serum AUC of naltrexone is about three times greater than that achieved by 50 mg/day oral administration and wherein the biocompatible polymer is a polylactide-co-glycolide polymer.

Documents Submitted by Requester

Comer et al., 2002, "Depot Naltrexone: Long-Lasting Antagonism of the Effects of Heroin in Humans," *Psychopharmacology* 159(4): 351-360 (Ex. E)

Nuwayser et al., US Patent No. 7,157,102 (Ex. F)

Johnson et al., 2004, "A Pilot Evaluation of the Safety and Tolerability of Repeat Dose Administration of Long-Acting Injectable Naltrexone (Vivitrex®) in Patients with

Alcohol Dependence," *Alcoholism: Clinical and Experimental Research* 28(9): 1356-1361 (Ex. G)

Rubio et al., 2001, "Naltrexone Versus Acamprosate: One Year Follow-Up of Alcohol Dependence Treatment," *Alcohol & Alcoholism* 36(5): 419-425 (Ex. W)

Wright et al., US Patent 6,264,987 (Ex. N)

Newly Cited Documents

Tice et al. (2001, US Patent 6,306,425; reference A on attached PTO-892)

Kaiko et al. (2002, US Patent 6,375,957; reference B on attached PTO-892)

Breder et al. (US 2003/0157168; reference C on attached PTO-892)

Priority

Application 11/083,167 was filed on 3/17/05 and claims benefit of US provisional application 60/564,542, which was filed on 4/22/04. The '499 patent issued from the '167 application on 4/5/11. The '499 patent lists no other domestic-benefit or foreign-priority claims.

Patent Owner's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, 365(c), or 386(c) is acknowledged. Patent Owner has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 112(e).

The underlying '167 application adds material beyond the disclosure of the '542 provisional application (specifically, examples 3-5 at columns 18-20), so it is analogous to a continuation-in-part of that provisional application. See MPEP 2152.01 (analysis of effective filing date not changed by AIA and referencing MPEP 2133.01). "[A]ny claim that contains a limitation that is only supported as required by pre-AIA 35 U.S.C. 112,

first paragraph, by the disclosure of the CIP application will have the effective filing date of the CIP application." MPEP 2133.01. See also MPEP 2218:

> [W]here the patent for which reexamination is requested is a continuation-in-part of a parent application, the requester would notify the Office of the application number of the parent application and its status if the asserted substantial new question of patentability relates to a proposed rejection based on an intervening art and the question of whether the claimed subject matter in the patent has support in the parent application is relevant.

The '542 provisional application nowhere provides data demonstrating possession of the claimed increased serum AUC from the claimed range of naltrexone dose. Serum AUC is a calculation that depends on numerous factors. See, e.g., Tice et al. (2001, US Patent 6,306,425) at columns 13-14 (calculating actual and extrapolated AUC for various naltrexone formulations); Kaiko et al. (2002, US Patent 6,375,957) at Figure 10A and column 38, lines 29-50 (showing different AUC patterns for different doses of naltrexone); Breder et al. (US 2003/0157168) at paragraph 289 (Table 7, showing varying AUC in different patients over time). The person of ordinary skill in the art would therefore have understood the serum AUC of a given naltrexone formulation to be unpredictable over time, with different dosages, and in different patients. In the absence of experimental data, then, the skilled artisan would not have concluded that the '542 provisional application teaches the claimed three-fold (or 3.3-fold) increase relative to 50 mg/day oral administration of naltrexone.

Because the '542 provisional application does not provide support for the AUC limitation in the manner set forth in 35 U.S.C. 112, first paragraph, the '499 patent's effective filing date is its actual filing date, **3/17/05.**

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of pre-AIA 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) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3-5, and 12 are rejected under pre-AIA 35 U.S.C. 102(b) as being anticipated by Comer (2002, "Depot Naltrexone: Long-Lasting Antagonism of the Effects of Heroin in Humans," *Psychopharmacology* 159(4): 351-360; Ex. E) as evidenced by Nuwayser (2007, US Patent No. 7,157,102; Ex. F).

Comer teaches a method of treating heroin addicts seeking recovery (individuals in need of naltrexone) by injecting into the buttocks (i.e., parenterally administering) a depot formulation of a total of 384 mg naltrexone, which is within the '499 patent's claimed dosage range. (Page 351, column 2; page 352, column 2; page 354, column 1.) Comer demonstrates that the depot formulation provides elevated plasma levels of naltrexone for about 28 days, which is reasonably interpreted as a "long-acting formulation." (Figure 1; page 355, column 1.) Nuwayser is cited solely as evidence that Comer's depot formulation, DEPOTREX, comprises poly-L-(–)-lactide-co-glycolide (PLGA). (Figure 7; column 14, lines 26-49; column 19, lines 4-26.)

Claim 1 requires that the long-acting formulation results in a serum area under the curve (AUC) that is about three times greater than that achieved by 50 mg/day oral administration. Claim 5 requires an AUC about 3.3 times greater. Comer teaches administering the same composition in the same way as that recited in the '499 patent. As such, all results of that administration are inherent to the active step. MPEP 2112.02(II) instructs:

> Under the principles of inherency, if a prior art device, in its normal and usual operation, would necessarily perform the method claimed, then the method claimed will be considered to be anticipated by the prior art device. When the prior art device is the same as a device described in the specification for carrying out the claimed method, it can be assumed the device will inherently perform the claimed process.

Comer therefore inherently anticipates claims 1 and 5.

Regarding claims 3 and 4, Comer demonstrates release of naltrexone for about four weeks, which is also "at least two weeks." (Figure 1; page 355, column 1.)

Regarding claim 12, Comer teaches injection. (Page 354, column 1.)

Claims 1, 3-5, and 7-12 are rejected under pre-AIA 35 U.S.C. 102(a) as being anticipated by Johnson et al., 2004, "A Pilot Evaluation of the Safety and Tolerability of Repeat Dose Administration of Long-Acting Injectable Naltrexone (Vivitrex®) in Patients with Alcohol Dependence," *Alcoholism: Clinical and Experimental Research* 28(9): 1356-1361 (Ex. G).

Regarding claim 1, Johnson administers 400 mg naltrexone to individuals suffering from alcoholism and seeking at least temporary abstinence (i.e., in need of naltrexone) intramuscularly (i.e., parenterally) in a formulation comprising PLGA. (Abstract; page 1357, columns 1 and 2.)

Claim 1 requires that the long-acting formulation result in a serum area under the curve (AUC) that is about three times greater than that achieved by 50 mg/day oral administration. Claim 5 requires an AUC about 3.3 times greater. Johnson teaches administering the same composition in the same way as that recited in the '499 patent. As such, all results of that administration are inherent to the active step. See MPEP 2112.02(II). Johnson therefore inherently anticipates claims 1 and 5.

Regarding claims 3 and 4, Johnson administers depot naltrexone every month for four months, which is also "at least two weeks." (Figure 1; page 355, column 1.)

Regarding claims 7-9, Johnson administers depot naltrexone every month for four months, meaning each administration is provided "at least about 7 days after the first administration." Johnson provides the same formulation in all four administrations, which meets the requirements of claims 8 and 9.

Regarding claim 10, Johnson's treated individuals are afflicted by alcohol dependency. (Page 1357, column 2, "Patient Enrollment . . . .")

Regarding claim 11, Johnson does not teach providing an initial oral dose of naltrexone. (Page 1357, column 2, "Study Design . . . .")

Regarding claim 12, Johnson teaches injection. (Page 1357, column 2, "Study Design . . . .")

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 negated by the manner in which the invention was made.

The factual inquiries 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.

Claims 2, 6-11, and 13 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Comer (Ex. E) in view of Nuwayser (Ex. F).

Comer teaches a method of treating heroin addicts seeking recovery (individuals in need of naltrexone) by injecting into the buttocks (i.e., parenterally administering) a depot formulation of a total of 384 mg naltrexone, which is within the '499 patent's claimed dosage range. (Page 351, column 2; page 352, column 2; page 354, column 1.) Comer demonstrates that the depot formulation provides elevated plasma levels of naltrexone for about 28 days, which is reasonably interpreted as a "long acting formulation." (Figure 1; page 355, column 1.) Nuwayser is cited as evidence that Comer's depot formulation, DEPOTREX, comprises poly-L-(–)-lactide-co-glycolide (PLGA). (Figure 7; column 14, lines 26-49; column 19, lines 4-26.)

Regarding claims 2 and 6, Comer does not exemplify administering the depot formulation every four weeks for at least about 24 weeks. Regarding claims 7-9, Comer does not exemplify administration at least every week of a substantially similar or identical formulation. Regarding claim 10, Comer does not exemplify treating individuals afflicted by alcohol dependency with depot naltrexone. Regarding claim 11, Comer does not exemplify omitting a preliminary dose of oral naltrexone before beginning treatment. Regarding claim 13, Comer does not specify that the long-acting formulation contains about 35% naltrexone by weight.

Regarding claims 2 and 6, Comer teaches administering naltrexone for over a year does not result in the development of tolerance to its antagonist effects. (Page 351, column 2.) The person of ordinary skill in the art would therefore have found it obvious to administer Comer's depot naltrexone for about 24 weeks or more in order to provide prolonged antagonism of the effects of heroin.

Regarding claims 7-9, Comer discloses that the depot formulation provides increased mean plasma levels of naltrexone for 28 days (Figure 1, left panel) and also teaches that compliance with oral-dosage regimens is low (page 351, column 1, through page 352, column 2). Comer discloses, however, that providing naltrexone for over a year can help manage heroin dependence. (Page 351, column 1.) The person of ordinary skill in the art would therefore have found it obvious to repeat Comer's administration of depot naltrexone in PLGA, for example every 28 days (which is "at least about 7 days"), in order to provide prolonged management of heroin dependence.

Regarding claim 10, Comer discloses that depot naltrexone is useful for treating individuals afflicted with alcohol dependency and that it "significantly reduced the

percentage of heavy drinking days in alcoholics" in an earlier study. (Page 352, column 1.) The person of ordinary skill in the art would therefore have found it obvious to use Comer's method to treat an individual afflicted by alcohol dependency in order to assist that individual with managing his or her addiction.

Regarding claim 11, Comer discloses "a treatment setting where oral naltrexone may not be given prior to depot naltrexone administration" and teaches methods for avoiding heroin-withdrawal symptoms when no preliminary dose of oral naltrexone is provided. (Page 359, column 2.) The person of ordinary skill in the art would therefore have understood an initial oral dose of naltrexone to be optional and would have found it obvious to omit that initial dose.

Regarding claim 13, Nuwayser teaches that DEPOTREX is made by mixing 10 grams of PLGA and 30 grams of naltrexone base in 120mL methylene chloride, then mixing with 2.7L of 10% polyvinyl alcohol (PVA) to make microspheres with 68.2% naltrexone. (Column 14, lines 26-49.) Nuwayser teaches that the microspheres are then coated with additional 1% PLGA solution for a "target coating level" of 14% to generate microcapsules with 54.4% naltrexone. (Column 19, lines 4-25.) Nuwayser teaches that the microparticle-manufacture method can make particles containing 0.1-80% of active ingredient or more by weight. (Column 4, lines 24-32.) The person of ordinary skill in the art would have understood that the concentration of naltrexone within the microparticles could be modified by changing the parameters of the manufacture method (concentration of reagents, desired coating level, etc.). Since these parameters are result-effective variables, it would have been obvious for the person of ordinary skill in

the art to optimize them through routine experimentation in order to arrive at a formulation containing about 35% naltrexone by weight. See MPEP 2144.05(II)(A).

Claims 2 and 6 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Johnson (Ex. G) in view of Rubio et al., 2001, "Naltrexone Versus Acamprosate: One Year Follow-Up of Alcohol Dependence Treatment," *Alcohol & Alcoholism* 36(5): 419-425 (Ex. W).

Johnson teaches administering 400 mg naltrexone to individuals suffering from alcoholism and seeking at least temporary abstinence (i.e., in need of naltrexone) intramuscularly (i.e., parenterally) in a formulation comprising PLGA monthly for four months (a total of four injections). (Abstract; page 1357, columns 1 and 2.)

Regarding claims 2 and 6, Johnson does not exemplify administering the depot formulation every four weeks for at least about 24 weeks.

Rubio teaches a randomized 12-month naltrexone treatment protocol in alcoholics. (Page 419, column 2, through page 420, column 1.) Rubio teaches that subjects who received the 12-month treatment showed improved abstinence, lack of relapse, and later relapse compared to those who received acamprosate. (Page 421, column 2; page 422, column 2.)

It would have been obvious for the person of ordinary skill in the art to continue administering Johnson's depot naltrexone for at least about 24 weeks because Rubio teaches that naltrexone can be administered for a year to provide prolonged assistance with managing alcohol dependence.

Claim 13 is rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Johnson (Ex. G) in view of Wright et al., US Patent 6,264,987 (Ex. N).

Johnson teaches administering 400 mg naltrexone to individuals suffering from alcoholism and seeking at least temporary abstinence (i.e., in need of naltrexone) intramuscularly (i.e., parenterally) in a formulation comprising PLGA monthly for four months (a total of four injections). (Abstract; page 1357, columns 1 and 2.) Johnson's formulation is known by the trade name MEDISORB. (Page 1357, column 1.)

Regarding claim 13, Johnson does not specify that the long-acting formulation contains about 35% naltrexone by weight.

Wright teaches methods for making MEDISORB naltrexone-loaded polymer containing 30-70% naltrexone by weight. (Column 7, line 63, through column 8, line 1.) Wright teaches that the drug-loading range is modified by selecting different amounts of drug and polymer. (Column 7, line 65, through column 8, line 1.)

The person of ordinary skill in the art would have understood that the concentration of naltrexone within Johnson's and Wright's microparticles could be modified by changing the parameters of the manufacture method (concentration of reagents.). Since these parameters are result-effective variables, it would have been obvious for the person of ordinary skill in the art to optimize them through routine experimentation in order to arrive at a formulation containing about 35% naltrexone by weight. See MPEP 2144.05(II)(A).

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 § 2146 *et seq.* 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 filing of a terminal disclaimer by itself is not a complete reply to a nonstatutory double patenting (NSDP) rejection. A complete reply requires that the terminal disclaimer be accompanied by a reply requesting reconsideration of the prior Office action. Even where the NSDP rejection is provisional the reply must be complete.

See MPEP § 804, subsection I.B.1. For a reply to a non-final Office action, see 37 CFR 1.111(a). For a reply to final Office action, see 37 CFR 1.113(c). A request for reconsideration while not provided for in 37 CFR 1.113(c) may be filed after final for consideration. See MPEP §§ 706.07(e) and 714.13.

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The actual 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/apply/applying-online/eterminal-disclaimer.

Claims 1-13 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1 and 14-18 of U.S. Patent No. 10,799,496 in view of Comer (2002, "Depot Naltrexone: Long-Lasting Antagonism of the Effects of Heroin in Humans," *Psychopharmacology* 159(4): 351-360; Ex. E) and Nuwayser (2007, US Patent No. 7,157,102; Ex. F). The '496 patent is assigned to Alkermes Pharma Ireland Ltd., as is the application under reexamination.

The '496 patent claims a pharmaceutical composition comprising naphthalene-containing prodrugs of naltrexone and a pharmaceutically acceptable carrier. (Claims 1 and 14.) The '496 patent's composition is adapted for parenteral administration, for example intramuscular injection. (Claims 15 and 18.) The '496 patent's composition provides naltrexone release for about 9 or about 13 weeks, i.e., it is long-acting.

The '496 patent does not specify that the composition comprises about 310-480 mg of naltrexone. The '496 patent does not specify that the pharmaceutically acceptable carrier is PLGA. The '496 patent does not indicate that the composition, upon administration, gives a serum AUC about three times greater than that achieved by 50 mg/day oral administration.

Comer teaches a method of treating heroin addicts seeking recovery (individuals in need of naltrexone) by injecting into the buttocks (i.e., parenterally administering) a depot formulation of a total of 384 mg naltrexone, which is within the reexamined '499 patent's claimed dosage range. (Page 351, column 2; page 352, column 2; page 354, column 1.) Comer demonstrates that the depot formulation provides elevated plasma levels of naltrexone for about 28 days, which is reasonably interpreted as a "long-acting formulation." (Figure 1; page 355, column 1.) Nuwayser teaches that Comer's depot formulation, DEPOTREX, comprises poly-L-(–)-lactide-co-glycolide (PLGA). (Figure 7; column 14, lines 26-49; column 19, lines 4-26.)

The person of ordinary skill in the art would have found it obvious to substitute Comer's naltrexone depot formulation for the composition of the '496 patent because both provide long-acting administration of naltrexone. The skilled artisan would have understood these formulations as being functional equivalents for each other. See MPEP 2144.06(II).

Comer's composition is identical to that recited in the '499 patent and is administered the same way. As such, all results of that administration are inherent to the active step. See MPEP 2112.02(II).

Regarding claims 2 and 6, Comer teaches administering naltrexone for over a year does not result in the development of tolerance to its antagonist effects. (Page 351, column 2.) The person of ordinary skill in the art would therefore have found it obvious to administer Comer's depot naltrexone for about 24 weeks or more in order to provide prolonged antagonism of the effects of heroin.

Regarding claims 3 and 4, both the '496 patent and Comer demonstrate release of naltrexone for about four weeks, which is also "at least two weeks." (Figure 1; page 355, column 1.)

Regarding claims 7-9, Comer discloses that the depot formulation provides increased mean plasma levels of naltrexone for 28 days (Figure 1, left panel) and also teaches that compliance with oral-dosage regimens is low (page 351, column 1, through page 352, column 2). Comer discloses, however, that providing naltrexone for over a year can help manage heroin dependence. (Page 351, column 1.) The person of ordinary skill in the art would therefore have found it obvious to repeat Comer's administration of depot naltrexone in PLGA, for example every 28 days (which is "at least about 7 days"), in order to provide prolonged management of heroin dependence.

Regarding claim 10, Comer discloses that depot naltrexone is useful for treating individuals afflicted with alcohol dependency and that it "significantly reduced the percentage of heavy drinking days in alcoholics" in an earlier study. (Page 352, column 1.) The person of ordinary skill in the art would therefore have found it obvious to use Comer's method to treat an individual afflicted by alcohol dependency in order to assist that individual with managing his or her addiction.

Regarding claim 11, Comer discloses "a treatment setting where oral naltrexone may not be given prior to depot naltrexone administration" and teaches methods for avoiding heroin-withdrawal symptoms when no preliminary dose of oral naltrexone is provided. (Page 359, column 2.) The person of ordinary skill in the art would therefore have understood an initial oral dose of naltrexone to be optional and would have found it obvious to omit that initial dose.

Regarding claim 12, both the '496 patent and Comer teach injection. (Page 354, column 1.)

Regarding claim 13, Nuwayser teaches that DEPOTREX is made by mixing 10 grams of PLGA and 30 grams of naltrexone base in 120mL methylene chloride, then mixing with 2.7L of 10% polyvinyl alcohol (PVA) to make microspheres with 68.2% naltrexone. (Column 14, lines 26-49.) Nuwayser teaches that the microspheres are then coated with additional 1% PLGA solution for a "target coating level" of 14% to generate microcapsules with 54.4% naltrexone. (Column 19, lines 4-25.) Nuwayser teaches that the microparticle-manufacture method can make particles containing 0.1-80% of active ingredient or more by weight. (Column 4, lines 24-32.) The person of ordinary skill in the art would have understood that the concentration of naltrexone within the microparticles could be modified by changing the parameters of the manufacture method (concentration of reagents, desired coating level, etc.). Since these parameters are result-effective variables, it would have been obvious for the person of ordinary skill in the art to optimize them through routine experimentation in order to arrive at a formulation containing about 35% naltrexone by weight. See MPEP 2144.05(II)(A).

Claims 1-13 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1 and 9-13 of U.S. Patent No. 10,807,995 in view of Comer (2002, "Depot Naltrexone: Long-Lasting Antagonism of the Effects of Heroin in Humans," *Psychopharmacology* 159(4): 351-360; Ex. E) and Nuwayser (2007, US Patent No. 7,157,102; Ex. F). The '995 patent is assigned to Alkermes Pharma Ireland Ltd., as is the application under reexamination.

The '995 patent claims a pharmaceutical composition comprising thienothiophene-containing prodrugs of naltrexone and a pharmaceutically acceptable carrier. (Claims 1 and 9.) The '995 patent's composition is adapted for parenteral administration, for example intramuscular injection. (Claims 10 and 13.) The '995 patent's composition provides naltrexone release for about 9 or about 13 weeks, i.e., it is long-acting. (Claims 11 and 12.)

The '995 patent does not specify that the composition comprises about 310-480 mg of naltrexone. The '995 patent does not specify that the pharmaceutically acceptable carrier is PLGA. The '995 patent does not indicate that the composition, upon administration, gives a serum AUC about three times greater than that achieved by 50 mg/day oral administration.

Comer teaches a method of treating heroin addicts seeking recovery (individuals in need of naltrexone) by injecting into the buttocks (i.e., parenterally administering) a depot formulation of a total of 384 mg naltrexone, which is within the reexamined '499 patent's claimed dosage range. (Page 351, column 2; page 352, column 2; page 354, column 1.) Comer demonstrates that the depot formulation provides elevated plasma levels of naltrexone for about 28 days, which is reasonably interpreted as a "long-acting

formulation." (Figure 1; page 355, column 1.) Nuwayser teaches that Comer's depot formulation, DEPOTREX, comprises poly-L-(–)-lactide-co-glycolide (PLGA). (Figure 7; column 14, lines 26-49; column 19, lines 4-26.)

The person of ordinary skill in the art would have found it obvious to substitute Comer's naltrexone depot formulation for the composition of the '995 patent because both provide long-acting administration of naltrexone. The skilled artisan would have understood these formulations as being functional equivalents for each other. See MPEP 2144.06(II).

Comer's composition is identical to that recited in the reexamined '499 patent and is administered the same way. As such, all results of that administration are inherent to the active step. See MPEP 2112.02(II).

Regarding claims 2 and 6, Comer teaches administering naltrexone for over a year does not result in the development of tolerance to its antagonist effects. (Page 351, column 2.) The person of ordinary skill in the art would therefore have found it obvious to administer Comer's depot naltrexone for about 24 weeks or more in order to provide prolonged antagonism of the effects of heroin.

Regarding claims 3 and 4, both the '995 patent and Comer demonstrate release of naltrexone for about four weeks, which is also "at least two weeks." (Figure 1; page 355, column 1.)

Regarding claims 7-9, Comer discloses that the depot formulation provides increased mean plasma levels of naltrexone for 28 days (Figure 1, left panel) and also teaches that compliance with oral-dosage regimens is low (page 351, column 1, through page 352, column 2). Comer discloses, however, that providing naltrexone for over a

year can help manage heroin dependence. (Page 351, column 1.) The person of ordinary skill in the art would therefore have found it obvious to repeat Comer's administration of depot naltrexone in PLGA, for example every 28 days (which is "at least about 7 days"), in order to provide prolonged management of heroin dependence.

Regarding claim 10, Comer discloses that depot naltrexone is useful for treating individuals afflicted with alcohol dependency and that it "significantly reduced the percentage of heavy drinking days in alcoholics" in an earlier study. (Page 352, column 1.) The person of ordinary skill in the art would therefore have found it obvious to use Comer's method to treat an individual afflicted by alcohol dependency in order to assist that individual with managing his or her addiction.

Regarding claim 11, Comer discloses "a treatment setting where oral naltrexone may not be given prior to depot naltrexone administration" and teaches methods for avoiding heroin-withdrawal symptoms when no preliminary dose of oral naltrexone is provided. (Page 359, column 2.) The person of ordinary skill in the art would therefore have understood an initial oral dose of naltrexone to be optional and would have found it obvious to omit that initial dose.

Regarding claim 12, both the '995 patent and Comer teach injection. (Page 354, column 1.)

Regarding claim 13, Nuwayser teaches that DEPOTREX is made by mixing 10 grams of PLGA and 30 grams of naltrexone base in 120mL methylene chloride, then mixing with 2.7L of 10% polyvinyl alcohol (PVA) to make microspheres with 68.2% naltrexone. (Column 14, lines 26-49.) Nuwayser teaches that the microspheres are then coated with additional 1% PLGA solution for a "target coating level" of 14% to generate

microcapsules with 54.4% naltrexone. (Column 19, lines 4-25.) Nuwayser teaches that the microparticle-manufacture method can make particles containing 0.1-80% of active ingredient or more by weight. (Column 4, lines 24-32.) The person of ordinary skill in the art would have understood that the concentration of naltrexone within the microparticles could be modified by changing the parameters of the manufacture method (concentration of reagents, desired coating level, etc.). Since these parameters are result-effective variables, it would have been obvious for the person of ordinary skill in the art to optimize them through routine experimentation in order to arrive at a formulation containing about 35% naltrexone by weight. See MPEP 2144.05(II)(A).

Claims 1-13 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1 and 9-13 of U.S. Patent No. 10,975,099 in view of Comer (2002, "Depot Naltrexone: Long-Lasting Antagonism of the Effects of Heroin in Humans," *Psychopharmacology* 159(4): 351-360; Ex. E) and Nuwayser (2007, US Patent No. 7,157,102; Ex. F). The '099 patent is assigned to Alkermes Pharma Ireland Ltd., as is the application under reexamination.

The '099 patent claims a pharmaceutical composition comprising thiophene-containing prodrugs of naltrexone and a pharmaceutically acceptable carrier. (Claims 1 and 9.) The '099 patent's composition is adapted for parenteral administration, for example intramuscular injection. (Claims 10 and 13.) The '099 patent's composition provides naltrexone release for about 9 or about 13 weeks, i.e., it is long-acting. (Claims 11 and 12.)

The '099 patent does not specify that the composition comprises about 310-480 mg of naltrexone. The '099 patent does not specify that the pharmaceutically acceptable carrier is PLGA. The '099 patent does not indicate that the composition, upon administration, gives a serum AUC about three times greater than that achieved by 50 mg/day oral administration.

Comer teaches a method of treating heroin addicts seeking recovery (individuals in need of naltrexone) by injecting into the buttocks (i.e., parenterally administering) a depot formulation of a total of 384 mg naltrexone, which is within the reexamined '499 patent's claimed dosage range. (Page 351, column 2; page 352, column 2; page 354, column 1.) Comer demonstrates that the depot formulation provides elevated plasma levels of naltrexone for about 28 days, which is reasonably interpreted as a "long-acting formulation." (Figure 1; page 355, column 1.) Nuwayser teaches that Comer's depot formulation, DEPOTREX, comprises poly-L-(–)-lactide-co-glycolide (PLGA). (Figure 7; column 14, lines 26-49; column 19, lines 4-26.)

The person of ordinary skill in the art would have found it obvious to substitute Comer's naltrexone depot formulation for the composition of the '099 patent because both provide long-acting administration of naltrexone. The skilled artisan would have understood these formulations as being functional equivalents for each other. See MPEP 2144.06(II).

Comer's composition is identical to that recited in the reexamined '499 patent and is administered the same way. As such, all results of that administration are inherent to the active step. See MPEP 2112.02(II).

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Conclusion

Claims 1-13 of US Patent 7,919,499 are rejected.

A shortened statutory period for reply to this action is set to expire TWO MONTHS from the mailing date of this action. Failure to respond within the period for response will result in termination of the proceeding and issuance of an ex parte reexamination certificate in accordance with this action. 37 CFR 1.550(d).

In order to ensure full consideration of any amendments, affidavits or declarations, or other documents as evidence of patentability, such documents must be submitted in response to this Office action. Submissions after the next Office action, which is intended to be a final action, will be governed by the requirements of 37 CFR 1.116, after final rejection and 37 CFR 41.33 after appeal, which will be strictly enforced.

Patent Owner Amendment

Patent owner is notified that any proposed amendment to the specification and/or claims in this reexamination proceeding must comply with 37 CFR 1.530(d)-(j), must be formally presented pursuant to 37 CFR 1.52(a) and (b), and must contain any fees required by 37 CFR 1.20(c).

Service of Papers

After the filing of a request for reexamination by a third-party requester, any document filed by either the patent owner or the third-party requester must be served on the other party (or parties where two or more third-party requester proceedings are merged) in the reexamination proceeding in the manner provided by 37 CFR 1.248. See 37 CFR 1.550(f).

Ongoing Duty to Disclose

The patent owner is reminded of the continuing responsibility under 37 CFR 1.565(a) to apprise the Office of any litigation activity, or other prior or concurrent proceeding, involving Patent No. 7,919,499 B2 throughout the course of this reexamination proceeding. See MPEP §§ 2207, 2282 and 2286. The third party requester is also reminded of the ability to similarly apprise the Office of any such activity or proceeding throughout the course of this reexamination proceeding. See MPEP §§ 2207, 2282 and 2286.

Extension of Time

Extensions of time under 37 CFR 1.136(a) will not be permitted in these proceedings because the provisions of 37 CFR 1.136 apply only to "an applicant" and not to parties in a reexamination proceeding. Additionally, 35 U.S.C. 305 requires that *ex parte* reexamination proceedings "will be conducted with special dispatch" (37 CFR 1.550(a)). Extensions of time in *ex parte* reexamination proceedings are provided for in 37 CFR 1.550(c).

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to LORA E BARNHART DRISCOLL, whose telephone number is (571) 272-1928. The examiner can normally be reached M-F 7:00-4:00 p.m. ET.

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, Timothy Speer, can be reached on 313-446-4825. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of published or unpublished applications may be obtained from Patent Center. Unpublished application information in Patent Center is available to registered users. To file and manage patent submissions in Patent Center, visit: https://patentcenter.uspto.gov. Visit https://www.uspto.gov/patents/apply/patent-center for more information about Patent Center and https://www.uspto.gov/patents/docx for information about filing in DOCX format. For additional questions, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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