

Request for *Ex Parte* Reexamination of
U.S. Patent No. 7,919,499

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent of: Elliot Ehrich
U.S. Patent No.: 7,919,499
Issue Date: April 5, 2011
Filing Date: March 17, 2005
For: Naltrexone long acting formulations and methods of use

Mail Stop *Ex Parte* Reexamination
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

**REQUEST FOR EX PARTE REEXAMINATION
PURSUANT TO 35 U.S.C. § 302 and 37 C.F.R. § 1.510 OF
U.S. PATENT NO. 7,919,499**

Commissioner of Patents:

Reexamination is requested under 35 U.S.C. §§ 302-307. The undersigned requests *ex parte* reexamination of claims 1-13 ("Challenged Claims") of U.S. Patent No. 7,919,499 ("the '499 patent"), that issued on April 5, 2011, to Elliot Ehrich and assigned to Alkermes Pharma Ireland Ltd.

The invalidity grounds presented herein are not cumulative of the prior art and grounds of record in the prosecution history of the '499 patent. Further, the new prior art references relied upon in the presented invalidity grounds are material and address all of the limitations of the Challenged Claims.

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For the reasons set forth below, Requester respectfully submits that at least one Substantial New Question of Patentability exists based upon prior art references submitted herewith.

Ex Parte Patent Reexamination Filing Requirements

Pursuant to 37 C.F.R. § 1.510(b)(1), statements pointing out at least one substantial new question of patentability ("SNQ") based on material, non-cumulative reference patents and printed publications are provided in Section IV of this Request.

Pursuant to 37 C.F.R. §§ 1.510(b)(2)-(3), reexamination of the Challenged Claims is requested, and a detailed explanation of the pertinence and manner of applying the prior art references to the Challenged Claims is provided in Section X of this Request. Copies of every patent or printed publication relied upon, or referred to, in the statement pointing out each SNQ and/or in the detailed explanation of the pertinence and manner of applying the prior art references are provided with this Request.

Pursuant to 37 C.F.R. §1.510(b)(4), a copy of the '499 Patent is provided as Exhibit A, along with a copy of any disclaimer, certificate of correction, or reexamination certificate issued in the patent. A copy of the file history of the '499 Patent is attached as Exhibit B.

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Pursuant to 37 C.F.R. §1.510(b)(5), the attached Certificate of Service indicates that a copy of this Request, in its entirety, including all of the Exhibits, has been served on Patent Owner at the following correspondence address of record:

Elmore Patent Law Group
484 Groton Road
Westford, MA 01886

Pursuant to 37 C.F.R. §1.510(b)(6) Requester certifies that the statutory estoppel provisions of 35 U.S.C. §§ 315(e)(1) and 325(e)(1) do not prohibit Requester from filing this *ex parte* patent reexamination request.

The attached transmittal document provides the additional filing information and acknowledgement of payment of the fee under 37 C.F.R. § 120(c)(1).

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A	U.S. Patent No. 7,919,499 (“’499 Patent”)
B	File history of the ’499 Patent
C	U.S. Provisional Application No. 60/564,542 (“the Provisional Application”)
D	Serial No. 11/083,167, Declaration Under 37 C.F.R. § 1.132 of Elliot Ehrich (undated)
E	Sandra D. Comer <i>et al.</i> , <i>Depot naltrexone: long-lasting antagonism of the effects of heroin in humans</i> , 159(4) <i>Psychopharmacology</i> (Feb. 2002), at 351-360. (“Comer”)
F	U.S. Patent No. 7,157,102 (“Nuwayser”)
G	Johnson <i>et al.</i> , “A Pilot Evaluation of the Safety and Tolerability of Repeat Dose Administration of Long-Acting Injectable Naltrexone (Vivitrex®) in Patients With Alcohol Dependence,” <i>Alcoholism: Clinical and Experimental Research</i> , Vol. 28, No. 9, 2004: 1356-1361. (“Vivitrex Pilot Study”)
H	Declaration of Kinam Park, Ph.D. of April 19, 2018 in IPR2018-00943
I	Synopsis, Naltrexone HCl, ALZA Corporation (Nov. 3, 2003)
J	In-hwan Baek <i>et al.</i> , <i>Evaluation of the Bioequivalence of Two Brands of Naltrexone 50 mg Tablet in Healthy Volunteers</i> , 16(1) <i>Kor. J. Clin. Pharm.</i> (2006), at 69-74
K	Institution Decision (Paper 8) IPR2018-00943
L	Decision Granting Joint Motion to Terminate (Paper 29) IPR2018-00943
M	U.S. Patent No. 6,306,425 (“Tice”)
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O	U.S. Serial Number 11/083,167, Office Action, May 5, 2009
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Q	U.S. Serial Number 11/083,167, Office Action, Jan. 6, 2010
R	U.S. Serial Number 11/083,167, Amendment and Response, Apr. 5, 2010
S	U.S. Serial Number 11/083,167, Final Rejection, July 20, 2010
T	U.S. Serial Number 11/083,167, Amendment After Final, Oct. 20, 2010
U	U.S. Serial Number 11/083,167, Notice of Allowance, Dec. 1, 2010
V	Henry R. Kranzler <i>et al.</i> , <i>Sustained-Release Naltrexone for Alcoholism Treatment: A Preliminary Study</i> , 22(5) <i>Alcoholism: Clinical and Experimental Research</i> (Aug. 1998), at 1074-79
W	G. Rubio <i>et al.</i> , <i>Naltrexone Versus Acamprosate: One Year Follow-Up of Alcohol Dependence Treatment</i> , 36(5) <i>Alcohol & Alcoholism</i> (2001), at 419-425
X	Filing Details for Alkermes Inc. 10-K dated July 1, 2002 from the Security and Exchange Commission's EDGAR Online Filing System
Y	U.S. Trademark Application Serial Number 76/271,990, Allegation of Use of a Mark & specimen of the mark as used in commerce, Aug. 15, 2002 ("Vivitrex Specimen" or "Specimen")
Z	Appeal Brief, Application No. 13/871,534, Oct. 19, 2015
AA	Joint Motion to Terminate (Paper 27) IPR2018-00943
BB	Joint Request to Treat Settlement and License Agreement as Business Confidential (Paper 28) IPR2018-00943
CC	Claims Chart

I. INTRODUCTION

The '499 Patent claims methods of treating addiction by parenterally administering 310-480 mg of a long-acting formulation comprising naltrexone and the biocompatible polymer polylactide-co-glycolide ("PLGA"), also known as poly(lactic-co-glycolic acid). The application that issued as the '499 Patent was filed on March 17, 2005, claiming priority to U.S. Provisional Application No. 60/564,542 ("the Provisional Application") (Ex. C). Critical to allowance was a declaration (Ex. D) presented by Patent Owner Alkermes Pharma Ireland Limited ("Alkermes") by its sole named inventor, Dr. Ehrich, arguing that the crux of the invention resides in an "unexpected discovery" made during clinical trials that a 380 mg naltrexone formulation provided a greater area under the curve ("AUC") than resulted from 50 mg/day oral administration. But this alleged "discovery" was nothing new.

Naltrexone is an old compound that was first investigated in the 1980s to treat substance abuse. (Ex. E at 351-353.) The ability of naltrexone to treat alcoholism was identified by 1986 and reported clinically by 1992. (*Id.*). As naltrexone therapy commenced in human patients, and non-compliance problems began to arise based on daily dosing requirements, it became clear that long-acting dosage forms could potentially improve patient outcomes significantly. (*Id.*). As a result, companies

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began investigating long-acting dosage forms, and in the early 2000s, BioTek developed “Depotrex,” a long-acting naltrexone product including 384 mg of naltrexone in a biocompatible PLGA polymer, dosed once per month—i.e., the same regimen as recited in the Challenged Claims. A publication describing this Depotrex product, Comer, anticipates the challenge claims, as described herein.

The Challenged Claims are also anticipated by a publication describing a pilot study evaluating Alkermes’ Vivitrex (the original name for Vivitrol) (“Vivitrex Pilot Study”) (Ex. G). Although published after the filing date of the ’542 Provisional Application—i.e., the ’499 Patent’s alleged priority document—the Vivitrex Pilot Study is nonetheless prior art because the Challenged Claims are not adequately supported or enabled by the provisional application. “It is elementary patent law that a patent application is entitled to the benefit of the filing date of an earlier filed application only if the disclosure of the earlier application provides support for the claims of the later application, as required by 35 U.S.C. § 112.” *PowerOasis, Inc. v. T-Mobile USA, Inc.*, 522 F.3d 1299, 1306 (Fed. Cir. 2008).

Specifically, the ’542 Provisional Application omits the critical data necessary to show possession and enablement of the subject matter recited in the Challenged Claims. Challenged claim 1 of the ’499 patent requires a “serum AUC of naltrexone [that] is about three times greater than that achieved by 50 mg/day oral administration” for a dose containing “about 310 mg to about 480 mg of naltrexone

and a biocompatible polymer.” But the provisional application (and the ’499 Patent specification) contains no serum AUC data for a 50 mg/day oral administration, which is essential to compare a long-acting formulation to the 50 mg/day form as required by the claim. (Ex. H at ¶¶ 35-36, 42.)

The choice of this comparator data is critical. When assessing whether some value X is three times greater than a value Y, it is axiomatic that the value of Y must be known to make the assessment. Without Y, the answer is unknowable.

During prosecution, Patent Owner relied on data presented in the Ehrich declaration, which uses a specific 50 mg/day oral administration for comparator data, i.e. the value of “Y.” But when using other publicly available 50 mg/day comparator data, in other words, different values for “Y,” the same Alkermes formulation is no longer “about three times greater,” and, therefore, no longer meets the claim. (Ex. H at ¶¶ 39, 82; Ex. I; Ex. J.) In other words, the choice of “Y” makes *all the difference*.

Although the Patent Trial and Appeal Board (“Board”) tangentially encountered this issue before in IPR2018-00943, finding the related claim term was at least broad enough “to create a reasonable likelihood that it reads on the prior art,” the Office has not yet considered whether the full scope of the claim is properly supported and enabled by the underlying provisional application. (Ex. K at 10-12.)

If the Ehrich declaration data is used to limit the claim to specific 50 mg/day

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oral administration data, this limitation is not supported in the provisional application because the Ehrich declaration was not available at that time. If, instead, the claims are read more broadly to encompass other 50 mg/day oral administration data, yet again the provisional application (and the '499 Patent) does not support or enable the full scope of the Challenged Claims.

In either case, the Vivtrex Pilot Study is prior art.

Finally, the prior art in SNQ Grounds 1 and 3 in this Request for Reexamination were the subject of the prior IPR2018-00943 petition filed by a different party (Amneal Pharmaceuticals LLC) than the Requester here, which the Board instituted on all grounds. (Ex. K.) Thus, through instituting that prior petition, the Board has already determined that there is a reasonable likelihood that SNQ Grounds 1 and 3 would successfully render the claims unpatentable. *See* 35 U.S.C. §314(a). That prior Board decision, which applies a more rigorous standard of “reasonable likelihood” necessarily establishes that the same grounds would meet the less rigorous standard required for reexamination where it is merely required that an examiner would consider the art “important” in deciding patentability. Alkermes and the Petitioner in that proceeding settled before the oral hearing was held, and the Board terminated the proceeding on the basis of settlement. (Ex. L) (*see* Section V(C) below).)

Below, Requester establishes that the Challenged Claims of the '499 Patent

are unpatentable under 35 U.S.C. §§ 102 and 103 as shown by Comer, the Vivitrex Pilot Study, and other art.

II. LEGAL STANDARD

In general, a "substantial question of patentability" exists when "there is a substantial likelihood that *a reasonable examiner would consider the prior art patent or printed publication important* in deciding whether or not the claim is patentable." MPEP § 2242 (emphasis added).

A substantial *new* question of patentability exists when a reasonable examiner would consider the prior art relied upon in the request for reexamination to be "important" and "the same question of patentability" has not already been decided by: (1) a federal court in a final holding of invalidity (after all appeals), or (2) the Office in an earlier examination, review, reexamination, or supplemental examination. (*Id.*)

An SNQ can exist even when some (or all) of the prior art relied upon in the reexamination request was previously before the Office ("old art"): "In a decision to order reexamination made on or after November 2, 2002, reliance on "old art" does not necessarily preclude the existence of a substantial new question of patentability." (*Id.*) Moreover, the MPEP expressly states that a rejection is proper when the proposed rejection combines "old art" with prior art that was not previously before the Office. MPEP § 2258.01 (citing *In re Hiniker*, 150 F.3d 1362, 1362 (Fed. Cir.

1998)) (“If the rejection to be made by the examiner will be *based on a combination of “old art” and art newly cited* during the reexamination proceeding, the rejection *is proper, and should be made.*” (emphasis added)).

A request only needs to identify an SNQ with respect to one challenged claim for reexamination to be ordered. (*Id.*) Furthermore, it is not necessary that a request for reexamination establish a *prima facie* case of unpatentability with respect to the challenged claims. (*Id.*) A SNQ can exist, “*even if the examiner would not necessarily reject the claim[s]* as either fully anticipated by, or obvious in view of the prior art” applied in a request. (MPEP § 2242 (citing *In re Etter*, 756 F.2d 852, 857 n.5 (Fed. Cir. 1985))).

Nevertheless, as shown in detail below, the prior art relied upon in each of the Grounds presented herein discloses each and every limitation of the Challenged Claims and thus would be “important in deciding whether or not the claim is patentable.”

III. IDENTIFICATION OF THE PATENT AND CLAIMS FOR WHICH REEXAMINATION IS REQUESTED

According to 35 U.S.C. § 302 and 37 C.F.R. § 1.510(B)(2), reexamination of claims 1-13 of the ’499 Patent is requested in view of the prior art references listed below. These claims may be referred to herein individually, or collectively as the “Challenged Claims” subject to reexamination.

Request for *Ex Parte* Reexamination of
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The '499 Patent issued on April 5, 2011, from U.S. Application Serial No. 11/083,167 (“the '167 Application”), filed on March 17, 2005, and claims the benefit of U.S. Provisional Application No. 60/564,542, filed April 22, 2004. (Ex. C.) Accordingly, the earliest possible effective filing date for the '499 Patent is April 22, 2004, but as explained at Sections I and V, the challenged claims are not entitled to the priority date of the provisional application.

Reexamination of claims 1-13 of the '499 Patent is requested in view of the following prior art patents and printed publications:

Exhibit	Description
E	Comer, Sandra D. et al., "Depot Naltrexone: Long-lasting Antagonism of the Effects of Heroin in Humans," <i>Psychopharmacology</i> , 159:351-360 (2002). (“Comer”) A copy of Comer bearing a library date stamp of February 18, 2002, and declaration of the British Library Board are provided. Comer is 35 U.S.C. § 102(b) prior art. Comer was of record but was not applied.
F	U.S. Patent No. 7,157,102 (“Nuwayser”). Nuwayser was filed on May 31, 2002, with a nonpublication request. Nuwayser is prior art under 35 U.S.C. § 102(e). Nuwayser was not of record.
G	Johnson et al., “A Pilot Evaluation of the Safety and Tolerability of Repeat Dose Administration of Long-Acting Injectable Naltrexone (Vivitrex®) in Patients With Alcohol Dependence,” <i>Alcoholism: Clinical and Experimental Research</i> , Vol. 28. No. 9, 2004: 1356-1361. (“Vivitrex Pilot Study”)
N	U.S. Patent No. 6,264,987 (“Wright”). Wright was published on July 24, 2001. It is prior art under 35 U.S.C. § 102(e). Wright was of record, but not discussed during prosecution.

W	Rubio, G. et al., NALTREXONE VERSUS ACAMPROSATE: ONE YEAR FOLLOW-UP OF ALCOHOL DEPENDENCE TREATMENT, Alcohol and Alcoholism, Volume 36, Issue 5, September 2001, Pages 419–425 (“Rubio”) A copy of Rubio bearing a library date stamp of September 28, 2001, is provided. Rubio is 35 U.S.C. § 102(b) prior art. Rubio was not of record or considered by the Examiner during prosecution.
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A Form SB-08 and copies of the foregoing references are submitted herewith.

Reexamination of the challenged claims is requested in view of the following grounds:

SNQ Ground	35 U.S.C.	Claims	References
1	102(b)	1, 3-5, 12	Comer
2	102(a)	1, 3-5, 10-12	Vivitrex Pilot Study
3	103(a)	1-13	Comer in view of Nuwayser, Rubio, and Wright
4	103(a)	1-13	Vivitrex Pilot Study in view of Comer, Rubio, and Wright.

IV. STATEMENT POINTING OUT EACH SUBSTANTIAL NEW QUESTION OF PATENTABILITY

For claims 1, 3-5, and 12 this Request presents a substantial new question of patentability based on anticipation under 35 U.S.C. § 102(b) over Comer, as evidenced by Nuwayser (“SNQ 1”). Comer describes each element claimed, including the allegedly unexpected AUC. Nuwayser supports what a person of

ordinary skill in the art (“POSA”) would understand from Comer’s reference to “Depotrex.”

As set forth in greater detail below, this Request presents a second substantial new question of patentability because the Vivitrex Pilot Study (“SNQ 2”) anticipates claims 1, 3-5, and 10-12 under 35 U.S.C. § 102(a). The Vivitrex Pilot Study similarly describes each element claimed. Additionally, the Vivitrex Pilot Study is prior art to the ’499 Patent because the patent is not entitled to the priority date of the provisional application. The Vivitrex Pilot Study describes each element claimed and would have anticipated the claims for the same reasons as Comer.

Furthermore, combinations of the primary references with secondary prior art references render claims of the ’499 Patent obvious. This Request presents a third substantial new question of patentability of claims 1-13 based on obviousness under 35 U.S.C. § 103 over Comer in view of Nuwayser, Rubio, and Wright (“SNQ 3”). This Request presents a fourth substantial new question of patentability of claims 1-13 based on obviousness over The Vivitrex Pilot Study in view of Comer, Rubio, and Wright (“SNQ 4”). The addition of Rubio and Wright to each of these SNQs establish that the dependent claims not challenged as being anticipated would have been obvious.

Requester submits that the prior art references raise a new “substantial question of patentability” because “the teaching of the (prior art) patents and printed

publications is such that a reasonable examiner would consider the teaching to be *important* in deciding whether or not the claim is patentable.” MPEP § 2242. As noted above, the Board in a prior IPR has already concluded that SNQ Grounds 1 and 3 are reasonably likely to render the claims unpatentable. Those same grounds here, in a reexamination context, would thus meet the lessened standard of being “important” in determining patentability.

Further, the additional grounds and references, discussed in further detail below, when considered independently (Vivitrex Pilot Study) or as a combination in view of their shared disclosures, teach each limitation of the claims. The Vivitrex Pilot Study discloses all limitations of the independent claim. Additionally, it would have been obvious to adjust the naltrexone dose in the Vivitrex Pilot Study (400 mg) to the dose used in Comer (384 mg) to arrive at yet another long-acting naltrexone formulation that produces the claimed AUC differential. The dependent claims are obvious based on the combination with Rubio and Wright as detailed further below.

Further, these prior art references are new because the “same question of patentability as to the claim has not been decided by the Office in an earlier concluded examination or review of the patent.” (*Id.*) Although some of the references (i.e., Comer and Wright) are of record, they were either not considered or not discussed by the Examiner during prosecution. On the other hand, neither Vivitrex Pilot Study, Rubio nor Nuwayser were raised, considered, or formed the

basis of a rejection during the original prosecution of the '499 Patent.

This Request provides the detailed mapping and explanation regarding the combination of references and raises a SNQ because the Office hasn't previously considered the teaching of the combinations of references in SNQ 1, SNQ 2, SNQ 3, or SNQ 4.

While Requester is not providing a separate declaration by an expert, given the overlapping grounds and positions presented herein, Requester cites to supportive testimony in the Park Declaration of April 19, 2018, from a prior IPR Petition in IPR2018-00943. (Ex. H.)

V. OVERVIEW OF THE '499 PATENT AND RELEVANT PROSECUTION HISTORY

A. Overview of the '499 Patent

The '499 Patent issued on April 5, 2011, from U.S. Application Serial No. 11/083,167 ("the '167 Application"), filed on March 17, 2005, and claims the benefit of U.S. Provisional Application No. 60/564,542, filed April 22, 2004. Accordingly, the earliest possible effective filing date for the '499 Patent is April 22, 2004, but as explained herein, the challenged claims are not entitled to the priority date of the provisional application.¹

The '499 Patent purports to describe a method of treating an individual in need

¹ Title 35 as it existed before adoption of the AIA is applicable here.

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of naltrexone by parenterally administering a long-acting formulation that includes 310-480 mg of naltrexone and PLGA to the individual, where the serum AUC of naltrexone is about three times greater than what is achieved by administration of 50 mg/day oral administration. (Ex. A at 1:30-46.)

The '499 Patent alleges that the “inventions described herein arose from unexpected discoveries made during clinical trials with a long-acting formulation of naltrexone.” (Ex. A at Abstract, 1:31-33; Ex. H at ¶ 15.) It provides no direct data for the AUC of any claimed formulation or the comparator—50 mg/day oral dosing. (Ex. A at 18:10-12; Ex. H at ¶ 35.) Nor does it discuss the duration under which the comparison should be made—one day, one week, one month, or something else. During prosecution, comparisons were made using data from an Alkermes’ study referenced in the '499 Patent and from Tice (Ex. M), but such comparisons were limited to a single duration, which is not included in the claims. In any event, none of this data could be determined from the patent or priority document itself.

The specification discusses the need for improving naltrexone therapies, based on patient compliance. (Ex. A at 1:13-26, 17:24-29; Ex. H at ¶ 16.) In some embodiments, the naltrexone is combined with well-known polymers, such as PLGA, to “entrap or encapsulate” the naltrexone and provide a long-acting formulation. (Ex. A at 3:14-15; Ex. H at ¶ 17.)

The specification describes its long-acting formulations as releasing

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naltrexone over a period of at least one week. (Ex. A at 3:59-64, 4:42-44.) It then describes “Vivitrex” as a monthly administration that releases naltrexone for four weeks, and that the therapy can be maintained for 24 weeks or more. (*Id.* 4:54-64.).

Five examples are included, three of which (Examples 3-5) were not present in the provisional application. (*Compare* Ex. A ('499 Patent) and Ex. C (Provisional Application).) Example 1 describes how to manufacture Vivitrex formulations. The microparticles portion of this example is virtually identical to the preparation described in Example 3 of Wright. (*Compare* Ex. A, 3:3-33, 5:35-8:2 and Ex. N, 7:50-8:60; Ex. H at ¶ 18.) The remaining examples describe various aspects of a clinical trial and meta-analysis. Example 2 describes screening, eligibility, and adverse events. (Ex. A at 8:5-18:2.) Newly added Example 3 compares the “efficacy” of oral versus injectable naltrexone but clearly states that “a direct head-to-head comparison of efficacy *has not been studied*” and thus “*a definitive comparison of efficacy between Vivitrex and oral naltrexone cannot be made.*” (Ex. A at 18:10-12; Ex. H at ¶¶ 19, 61.) Instead, the specification admits to using data from three nonrelated studies for a “semi-quantitative” comparison that resulted in efficacy that “compares favorably with oral naltrexone.” “Favorably” in this context would be understood by a POSA to mean comparable or equivalent to, as the '499 Patent's data would not establish improved efficacy to a POSA. (Ex. H at ¶¶ 16, 61; Ex. A at 18:12-29, 19:30-33.) Finally, newly added Examples 4 and 5 are directed

to “quality of life” and “durability of effect and tolerability” of long-acting naltrexone formulations.

B. Relevant Prosecution History of the '499 Patent

The '499 Patent was filed with a request for prioritized examination under 37 C.F.R. § 1.102(e) on March 17, 2005, as the '167 Application. On September 5, 2007, Alkermes filed a preliminary amendment, which merely canceled original claims 24 and 25. A restriction requirement was mailed on February 20, 2009, and Alkermes responded on March 20, 2009, electing Group 1, *i.e.*, claims 1, 2, and 6-23, with traverse.

A nonfinal rejection was mailed on May 5, 2009 (Ex. O), which rejected the claims as allegedly being anticipated by Tice and, in the alternative, as being obvious over the combination of Tice and Chandrashekar. Alkermes responded on October 5, 2009 (Ex. P), with claim amendments and a declaration under 37 C.F.R. § 1.132 by Elliot Ehrich (the “Ehrich Declaration” (Ex. D)), the sole inventor of the '499 Patent. The Ehrich Declaration argued that Tice used polylactic acid (“PLA”), not PLGA, and that the AUC of Tice’s formulation was about the same as that of 50 mg/day oral dosing. In contrast, the claimed invention allegedly resulted in 3.3 times the oral AUC. Alkermes also argued the existence of this AUC differential using its own oral data from a clinical trial, not information from the patent specification. (Ex. H at ¶¶ 23, 63, 72-74.)

The Examiner issued a second office action on January 6, 2010, which withdrew the anticipation and obviousness rejections over Tice in view of the Ehrich Declaration but nevertheless rejected the claims for lack of enablement. (Ex. Q.) Alkermes responded on April 5, 2010, by amending the claims to require a biocompatible polymer. (Ex. R.) A final rejection was mailed on July 20, 2010, maintaining the enablement rejection. (Ex. S.) Alkermes filed a response after final on October 20, 2010, amending the claims further to require that the biocompatible polymer be PLGA. (Ex. T; Ex. H at ¶ 23.)

A Notice of Allowance was mailed on December 1, 2010, which acknowledged a telephone interview of November 19, 2010, where Alkermes agreed to an Examiner's Amendment to insert certain language into the claims, *e.g.*, “about 310 mg to about 480 mg” into claim 1. (Ex. U.) The Examiner also included reasons for allowance. According to the Examiner, Tice was the closest prior art and reported that its injectable formulation was comparable to taking 50 mg tablets orally. (*Id.*)

But, as discussed below, Tice is not the closest prior art. (Ex. H at ¶ 24.)

C. Prior IPR Proceeding

On April 20, 2018, Amneal Pharmaceuticals LLC (“Amneal”) filed and served an IPR petition against Alkermes Pharma Ireland Limited (“Alkermes”) regarding U.S. Patent No. 7,919,499 (IPR2018-00943 (“the ‘943 IPR”)). Finding that Petitioner had demonstrated a reasonable likelihood of success in proving

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at least one claim of the '499 patent was unpatentable and to that end that the elements of the claims were taught by the prior art, the Board instituted the '943 IPR on November 7, 2018. (Ex. K at 2.)

Amneal's '943 IPR petition identified six grounds that purported to render the claims of the '499 patent unpatentable as anticipated or obvious in view of the cited references. Amneal alleged that the '499 patent is anticipated. Specifically, the '943 IPR identified claims 1, 3-5, and 10-12 as anticipated by Comer, as evidenced by Nuwayser and additionally identified claims 1, 3-5, and 11-12 as anticipated by Nuwayser, which, Amneal argued similarly describes each element claimed and discloses the claimed dose to a POSA by integration of the blood level plot in Figure 7 of Nuwayser.

Next, Amneal asserted that even if the claims are not anticipated, all of the challenged claims are obvious over Comer in view of Nuwayser, Rubio, and Wright; and Nuwayser in view of Comer, Rubio, and Wright. Amneal also alleged that the challenged claims are obvious over Nuwayser in view of Kranzler (Ex. V), Rubio (Ex. W), and Wright (Ex. N). Further, Amneal noted that Rubio and Wright are applicable to dependent claims 2, 6, and 13. And finally, Amneal contended that all of the challenged claims are obvious over Alkermes' 10-K (Ex. X) in view of the Vivitrex® Trademark Specimen (Ex. Y), Rubio, and Wright, again noting that Wright and Rubio are also applicable to dependent claims 2, 6, and 13.

Amneal's '943 IPR proceeded all the way through briefing to the day set for the oral hearing, July 29, 2019. (Ex. K.) On July 29, 2019, the Board authorized the parties to file a Joint Motion to Terminate, and the next day, the parties filed a Joint Motion to Terminate based on settlement. (Ex. AA and Ex. BB.) On July 31, 2019, the Board granted the Motion to Terminate. (Ex. L.) Thus, no final written decision was issued in the '943 IPR.

**VI. THIS REEXAMINATION REQUEST SHOULD NOT BE DENIED
UNDER 35 U.S.C. § 325(d)**

Reexamination should not be denied on the basis that the art presented here was used during the prosecution of the '499 patent as none of the references used to support the grounds of this petition (Comer, Nuwayser, Vivitrex Pilot Study, Rubio, and Wright) were used by the Office to reject the claims during prosecution. Only Comer and Wright were of record and are listed on the face of the '499 patent, but neither were applied by the Examiner during prosecution.

The '943 IPR, filed by a different party, should not prevent the grant of this request for reexamination as that IPR did not go to final written decision. Moreover, while both the '943 IPR and this Request use some of the same prior art (Comer, Nuwayser, Rubio, and Wright), additionally presented arguments rely on prior art and positions that were not at issue in the prior IPR (Vivitrex Pilot Study and inherency arguments). Further, the Requester of Reexamination here ("Argentum")

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is a different and entirely unrelated entity from the petitioner in the '943 IPR, Amneal Pharmaceuticals LLC and did not cooperate with or have any contact with Amneal in the '943 IPR. Requester has never filed a proceeding against U.S. Patent No. 7,919,499, including *inter partes* review proceedings.

For these reasons, this Request should not be denied under 35 U.S.C. § 325(d).

VII. LEVEL OF ORDINARY SKILL IN THE ART

Factors relevant to determining the level of skill in the art include: the educational level of the inventors, the types of problems encountered in the art, prior art solutions to those problems, the rapidity with which innovations are made, the sophistication of the technology, and the educational level of active workers in the field. *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1373, 1376 (Fed. Cir. 2012).

While the claims here are to a method of medical treatment, all of the elements of that method are well documented in the art and understandable by anyone with at least a college education. (Ex. H at ¶¶ 28-31.) However, given that the discussion of patentability during prosecution related to pharmacokinetics, which is ordinarily the province of Pharm.Ds and Ph.Ds in pharmaceuticals and related formulation sciences, a POSA for these claims would have such a doctorate level degree in one of these disciplines and at least two years of experience in controlled release formulation. A lesser degree of formal education balanced by additional practical experience could also qualify as a POSA. (Ex. H at ¶¶ 28-31.)

VIII. CLAIM CONSTRUCTION

In reexamination proceedings, claims are given “their broadest reasonable interpretation, consistent with the specification.” *In re Yamamoto*, 740 F.2d 1569, 1571 (Fed. Cir. 1984). Requester provides the following comments regarding certain terms of the ’499 Patent.

A. “a long acting formulation”

The claims require “a long acting” formulation. The ’499 Patent states that “long acting” may also be referred to as “extended, sustained, or controlled release” preparations and defines “long acting” as delivering “therapeutically beneficial amounts of naltrexone to a patient for a period of at least one week.” (Ex. A at 3:11-13, 3:59-64; Ex. H at ¶ 34.)

The indefinite article “a,” when recited in a claim, means “one or more.” *See Baldwin Graphic Sys., Inc. v. Siebert, Inc.*, 512 F.3d 1338, 1342 (Fed. Cir. 2008) (“That ‘a’ or ‘an’ can mean ‘one or more’ is best described as a rule, rather than merely as a presumption or even a convention.”) Ignoring the rule, Alkermes in IPR2018-00943 attempted to limit “a long acting formulation” to a “single injection” or a single shot. (IPR2018-00943 at Paper 14, at 5-7). While Alkermes argued the “specification and prosecution history” support this interpretation, Alkermes was simply grasping at straws. There is nothing in either that supports the “extremely limited” exception to the general rule that “a” means “one or more.” (IPR2018-

00943, Paper 14 at 5-7); *see Baldwin*, 512 F.3d at 1342 (“The exceptions to this rule are extremely limited: a patentee must ‘evince a clear intent’ to limit ‘a’ or ‘an’ to ‘one.’”) (citing *KCJ Corp. v. Kinetic Concepts, Inc.*, 223 F.3d 1351, 1356 (Fed. Cir. 2000)).²

B. “the serum AUC of naltrexone...than that achieved by 50 mg/day oral administration”

The claims require a “serum AUC,” but “serum AUC” is not defined by the specification. A POSA would appreciate that this refers to serum “area under the curve.”³ . A POSA would clearly know the meaning of AUC and how it is determined. (Ex. H at ¶¶ 36-37, 56-59.) Briefly, AUC is merely the area under a curve created by plotting plasma drug concentration versus time. (*Id.* ¶¶ 38, 56, 69, 73.) So long as the minimum therapeutic blood levels are maintained, the treatment will be effective regardless of AUC. (*Id.* ¶¶ 38, 60.) Indeed, a higher AUC could indicate unnecessary exposure to the drug. (*Id.* ¶ 60.)

The ’499 Patent also lacks a definition of “about three times greater than that achieved by 50 mg/day oral administration,” found in the claims. The problem here

² The application of the Philips claim construction standard in IPR2018-00943 does not change the calculus here in this reexamination proceeding. Under the BRI standard, there is nothing that supports the “extremely limited” exception to the general rule that “a” means “one or more.”

³ The Board previously construed this term in IPR2018-00943, and Requester’s constructions are consistent with that determination. The construction remains the same under the BRI standard. (Ex. K at 8.)

is not with the literal wording but with the fact that no data is provided in the specification to establish the AUC of the claimed formulation or the AUC of 50 mg/day oral dosing used for comparison. Instead, the '499 Patent merely makes unsubstantiated assertions about this relationship. (Ex. A at 1:36-40, 2:23-36; Ex. H at ¶¶ 35-47.)

The Board previously determined the reference to “50 mg/day” AUC in “than that achieved by 50 mg/day oral administration” encompasses “at least serum AUCs of 1.278 ng•day/ml and 1.468 ng•day/ml,” i.e., the data presented in the Ehrich declaration which encompassed the data from Tice and the Alkermes clinical study on Vivitrol. (Ex. K at 11-12). The BRI construction would be at least as broad as the construction applied by the Board and would capture at least those data points from the Ehrich declaration. In fact, this AUC comparator data must be the data used, otherwise the claims are indefinite because there are different sources of data that could be used as the 50 mg/day oral dosing data, and depending on which data is selected, the AUC differential calculation would be different. *Teva Pharmaceuticals USA, Inc. v. Sandoz, Inc.*, 789 F.3d 1335, 1341-45, 115 U.S.P.Q.2d 1210 (Fed. Cir. 2015) (holding that claims were indefinite where the claims required a specific measurement and more than one measurement method could be used, but the patent provided no guidance on which specific method to use); *see also, Otsuka Pharmaceutical Co., Ltd. v. Torrent Pharmaceuticals Limited, Inc.*, 151 F. Supp. 3d

525, 544-549 (D.N.J. 2015), *aff'd*, (Mar 15, 2017) 694 Fed. Appx. 808 (Fed. Cir. 2017) (holding claims indefinite where the term “mean particle size” is susceptible “to multiple measurements, each of which could yield varied results.”).

If the AUC data reported in Comer and Nuwayser are compared with the oral AUC data used in the Ehrich Declaration, *i.e.*, the data encompassed by this claim term, the resulting differential is about three times as claimed. (Ex. H at ¶¶ 66-77, 81, 89, 96.) The same result would come from the use of the Tice oral data, which again, was also described in the Ehrich Declaration. (*Id.*)⁴

Under the BRI claim construction standard, there is no logical basis to construe the term “about three times greater than that achieved by 50 mg/day oral administration” to exclude any particular 50 mg/day oral administration. This term therefore encompasses any such 50 mg/day administration, including the administrations described in the Ehrich declaration and Tice.

C. “about three”

Claim 1 requires “about three.” The term is not specifically defined in the ’499 Patent. 35 U.S.C. § 112, fourth paragraph, requires that a dependent claim further narrow the scope of the claim from which it depends. Here, claim 5 specifies an

⁴ On the other hand, using the data reported in Comer and Nuwayser for their depot injection against other published data for 50 mg/day oral dosing would result in an AUC differential (AUC_{0-28d}), which could be as low as 2.1 or as high as 5.3 times that of oral dosing. (Ex. H at ¶¶ 82-86.)

AUC of about 3.3 times greater than oral dosing. Thus, “about three” necessarily encompasses at least 3.3. This is further supported by the Ehrich Declaration that points to data indicating an AUC of 3.3 times greater than oral dosing as supporting the patentability of both claims 1 and 5.

A POSA would thus appreciate that “about three” also encompasses at least “about 2.7.” (Ex. H at ¶¶ 45-47.) The Board previously agreed that “about three” necessarily encompasses values as high as 3.3 and as low as 2.7. (Ex. H at ¶ 47) However, under a broadest reasonable interpretation, this term could encompass a wider range.

D. “five of more days”

Claim 2 requires that the individual not use oral naltrexone within five or more days before administration of the formulation. This was not the original language of the claim, as filed. The original language mirrors the language used in the specification, namely “has not used oral naltrexone within five days, such as within ten days, before said administration.” (Ex. A at 2:1-2.) Putting aside the fact that ten days is not within five days, the claim can either be read to encompass no prior oral naltrexone administration within five days or simply no prior oral naltrexone administration *ever*. The use of the phrase “or more” in the claim, and the attempt to define the concept as encompassing ten days, manifests an intention to cover a range greater than five days. Thus, the broadest reasonable interpretation encompasses no

prior oral naltrexone administration, *ever*.

E. “initial oral dose”

Claim 11 requires the individual not receive an “initial oral dose” of naltrexone. The ’499 Patent does not define this term. The only reference to dosing in the ’499 Patent is to the administration of naltrexone to treat a patient to overcome his or her addiction. The art, however, makes clear that there are other purposes. For example, Comer teaches the use of naltrexone as part of a detoxification process prior to treatment. (Ex. E at 353-354.) There is a break of two days between administering the detoxification doses and the treatment doses. (*Id.*) Similarly, a small percentage of the patient population can have serious adverse reactions to naltrexone. Naltrexone has been given orally to test for this prior to giving a depot injection for treatment. (Ex. M at 5:65-6:6, 6:13-17.) Clearly the art distinguishes initial treatment doses from prior doses given for other purposes. Accordingly, the broadest reasonable interpretation of “initial oral dose” as used in the ’499 Patent is an earlier *treatment* dose, not a dose provided for other purposes.

F. “about 35% by weight”

Claim 13 requires the long acting formulation be present at a concentration of about 35% by weight. The specification does not specifically define what is meant by “formulation,” but does describe how to produce the microparticles, *i.e.*, 30-75% drug loading. (Ex. A at 6:52-54.) A POSA would appreciate that this term refers to

the percent by weight of the particle. (Ex. H at ¶ 50.)

IX. OVERVIEW OF THE PRIOR ART

This Request establishes that the Challenged Claims are anticipated or obvious based on the teachings of Comer, Vivitrex Pilot Study, Nuwayser, Rubio, and Wright. During the original examination of the '499 Patent, the Examiner did not consider, discuss, or rely on any of the references.

A. Comer et al. (Exhibit E)

The study titled "Depot naltrexone: long-lasting antagonism of the effects of heroin in humans" evaluates the time course, safety, and effectiveness of a sustained-release formulation of naltrexone (Depotrex®) in heroin-dependent individuals. Conducted by Sandra D. Comer and colleagues from the Division on Substance Abuse at the New York State Psychiatric Institute and Columbia University, the study involved 12 participants who were administered either 192 mg or 384 mg of depot naltrexone following a one-week detoxification period. The effects of heroin were tested over six weeks.

The researchers administered Depotrex® containing 384 mg of naltrexone to human patients. (Ex. E at 353-54.) Comer reported that the 384-mg dose provided therapeutic blood plasma concentrations for longer than a competing lower dose. (*e.g.*, Ex. E at Fig 1). The report also included a chart (Fig. 1) demonstrating serum AUC for the 384 mg dose over the course of 35+ days, which exhibited about three

times greater serum AUC as compared to 50 mg/day oral naltrexone administration. Comer concluded that this “formulation of naltrexone that requires only once-a-month administration has important and exciting treatment implications.” (Ex. E at 359.) The study concludes that depot naltrexone is a safe and effective long-term treatment for heroin dependence, with potential to improve compliance due to its sustained-release formulation.

Comer was of record but was not applied by the Examiner during prosecution. A copy of Comer bearing a library date stamp of February 18, 2002, and declaration of the British Library Board are provided. Comer is a printed publication that is prior art under 35 U.S.C. § 102(b).

B. Vivitrex Pilot Study (Exhibit G)

The Vivitrex Pilot Study is directed to assessing the safety and tolerability of a long-acting injectable formulation of naltrexone (Vivitrex®) for treating alcohol dependence. Conducted across multiple centers, this randomized, double-blind, placebo-controlled study involved 30 patients who met DSM-IV criteria for alcohol dependence. Participants were administered either 400 mg of injectable naltrexone or a placebo every 28 days for four months, alongside psychosocial support.

The Vivitrex Pilot Study reports the design and results of the placebo-controlled pilot study to evaluate the safety and tolerability of intramuscular repeat dose administration of Vivitrex. (Ex. G at Abstract). Patients were injected with

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“Vivitrex®”—a 400 mg long-acting naltrexone formulation—or placebo once every 28 days over 4 months. (*Id.* at Abstract, 1357). Vivitrex is described as using “Medisorb®” extended-release drug delivery technology, using injectable, biodegradable microspheres as delivery medium. (*Id.* at 1357.) The microspheres were “composed of naltrexone incorporated into a matrix of polylactide-co-glycolide (PLG).⁵ (*Id.*)

Because the '499 Patent is not entitled to the priority date of the provisional application, the Vivitrex Pilot Study is prior art. Although published after the filing date of the '542 Provisional Application—i.e., the '499 Patent’s alleged priority document—the Pilot Study is nonetheless prior art because the challenged claims are not adequately supported or enabled by the provisional application. “It is elementary patent law that a patent application is entitled to the benefit of the filing date of an earlier filed application only if the disclosure of the earlier application provides support for the claims of the later application, as required by 35 U.S.C. § 112.” *PowerOasis, Inc. v. T-Mobile USA, Inc.*, 522 F.3d 1299, 1306 (Fed. Cir. 2008). Thus, the Vivitrex Pilot Study is a printed publication that is prior art under 35 U.S.C. § 102(a).

⁵ PLG is also known as PLGA.

C. U.S. Patent No. 7,157,102 (“Nuwayser”) (Exhibit F)

U.S. Patent No. 7,157,102 B1 granted on January 2, 2007, to Elie S. Nuwayser and assigned to Biotek, Inc. Nuwayser was filed on May 31, 2002, with a nonpublication request. Nuwayser is prior art under 35 U.S.C. § 102(e). Nuwayser was not of record during prosecution.

Nuwayser describes multi-layered microcapsules and methods for their preparation. These microcapsules are designed for the controlled release of active ingredients, such as drugs, over prolonged periods. The microcapsules consist of an inner solid microparticle core, typically made of a biodegradable polymer, and multiple alternating layers of polymer and active ingredients. The layers can vary in their composition and concentration, allowing for tailored release profiles.

The microcapsules have a core that may or may not contain active ingredients and are coated with alternating layers of polymers and active ingredients. The polymers used are biodegradable and biocompatible, such as polylactides (PLA), polyglycolides (PGA), and their copolymers. The core is prepared by solvent evaporation techniques, and the layers are applied using fluidized bed air suspension technology. The process allows for high drug loading and low residual solvent content. The microcapsules can deliver various pharmacologically active agents, including hormones, opioid antagonists, and other drugs, in a controlled manner. They are suitable for oral, intranasal, or parenteral administration.

Nuwayser provides detailed examples of preparing microcapsules with different drugs, such as progesterone, testosterone, *naltrexone*, nalmefene, and buprenorphine. These examples demonstrate the versatility and effectiveness of the microcapsules in achieving sustained drug release. Specifically, Nuwayser provides an example (Example IV, and Fig. 7) detailing a formulation containing naltrexone and PLGA that it identifies as “Depotrex.”

D. Rubio et al. (Exhibit W)

The study conducted by Rubio and colleagues, published in 2001 in “Alcohol & Alcoholism,” compares the efficacy of naltrexone and acamprosate in treating alcohol dependence over a one-year period. A copy of Rubio bearing a library date stamp of September 28, 2001, is provided. Rubio was not of record or considered by the Examiner during prosecution. Rubio is 35 U.S.C. § 102(b) prior art.

A total of 157 recently detoxified alcohol-dependent men were randomly assigned to receive either naltrexone (50 mg/day) or acamprosate (1665-1998 mg/day). The study aimed to evaluate the effectiveness of these treatments under conditions similar to routine clinical practice. Rubio observed that naltrexone was more effective in preventing relapse, with 41% of patients remaining relapse-free at the end of one year compared to 17% in the acamprosate group. The time to first relapse was significantly longer for naltrexone (63 days) compared to acamprosate (42 days). Patients on naltrexone had a greater cumulative number of days of

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abstinence, consumed fewer drinks at one time, and experienced less severe cravings. The study suggests that naltrexone may be more beneficial than acamprosate for long-term treatment of alcohol dependence, particularly in patients with moderate dependence.

E. U.S. Patent No. 6,264,987 (“Wright”) (Exhibit N)

U.S. Patent No. 6,264,987 was granted on July 24, 2001 to inventors Steven G. Wright, Michael E. Rickey, J. Michael Ramstack, Shawn L. Lyons, and Joyce M. Hotz, and assigned to Alkermes Controlled Therapeutics Inc. II. Thus, Wright qualifies as prior art under 35 U.S.C. § 102(e). Wright was of record, but not discussed by the Examiner during prosecution.

Wright describes a method for preparing microparticles with a controlled polymer molecular weight by manipulating the hold time and temperature of a solution containing a nucleophilic compound and a polymer. This method allows for the production of microparticles with a desired polymer molecular weight from various starting material molecular weights.

The first phase consists of a nucleophilic compound, a polymer with a starting molecular weight, and a solvent for the polymer. The first phase is combined with a second phase under mixing to form an emulsion. The emulsion is combined with an extraction medium to form microparticles. The molecular weight of the polymer in the microparticles is controlled by adjusting the hold time and temperature of the

first phase before combining it with the second phase.

Wright includes various embodiments and examples demonstrating the method, including the use of different polymers and nucleophilic compounds, and the effect of temperature on the molecular weight decay of the polymer.

X. SUBSTANTIAL NEW QUESTIONS OF PATENTABILITY

A. SNQ Ground 1: Claims 1, 3-5, and 12 are anticipated by Comer as evidenced by Nuwayser

Claim 1 is recited below, with elements noted by (a), (b), and (c). For ease of discussion, the last element is grouped with element (b).

(a) A method for treating an individual in need of naltrexone comprising the step of

(b) parenterally administering a long acting formulation comprising about 310 mg to about 480 mg of naltrexone and a biocompatible polymer to the individual

(c) wherein the serum AUC of naltrexone is about three times greater than that achieved by 50 mg/day oral administration and

(b) wherein the biocompatible polymer is a polylactide-co-glycolide polymer.

1. “A method for treating an individual in need of naltrexone”

Comer discloses a method for treating an individual in need of naltrexone. Comer describes its objective of the study as one that “was designed to evaluate the time course, safety, and effectiveness of a depot formulation of naltrexone (Depotrex®).” (Ex. E at 351.) The abstract further states that naltrexone “is

currently approved as a treatment for heroin dependence.” (*Id.*) The individuals selected for participation in the study were “heroin-dependent individuals,” and thus, were considered individuals in need of naltrexone, as required by the claim. (*Id.*) Comer also discusses how naltrexone was widely known for treating addicts and alcoholics, in oral and injectable forms. (Ex. E at 351-354.) Therefore, the study conducted by Comer is “treating” as recited in the claims. Patent Owner previously attempted to argue that Comer did not disclose “treating,” but this argument was rejected by the Board (Ex. K at Paper 8, at 28-29 (“Patent Owner’s argument that ‘[n]either reference discloses ‘treating’ someone ... lacks evidentiary support.’”).)

2. “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 biocompatible polymer is a polyactide-co-glycolide polymer”

Comer describes testing in human opioid-dependent patients of a depot injection made from 384 mg of naltrexone (Depotrex®). (Ex. E at 351-354.) “The active formulation contained drug equivalent to 192 mg naltrexone base...and for the high dose, participants received two naltrexone injections (384 [sic] mg naltrexone base).” (*Id.* at 354; Ex. H at ¶ 87.)

While not stated in Comer *per se*, a POSA would understand from, for example, Nuwayser, that Depotrex® is an extended-release microcapsule comprising naltrexone and PLGA. Anticipation can be established using a combination of

references where—as here—the secondary reference is used merely to establish the meaning of a term to a POSA. *In re Baxter Travenol Labs.*, 952 F.2d 388, 390-91 (Fed. Cir. 1991); *see also* MPEP § 2131.01 [I], [II]. In Example IV, Nuwayser describes a formulation containing 54.4% naltrexone in PLGA (65% lactide: 35% glycolide, or 65% LA: 35% GA), identified as “Depotrex.” When administered subcutaneously, Depotrex delivered therapeutic levels in six heroin addicts for 30 days. (Ex. F at 14:26-50, 19:4-25, Fig. 7.) In addition, a POSA would note the superimposable nature of the AUC plots provided in Figure 1 of Comer and Figure 7 of Nuwayser, which would only serve to underscore the identity of Depotrex referenced in Comer. (Ex. E at 354, Fig. 1; Ex. F at 19:4-25, Fig. 7; Ex. H at ¶¶ 77, 90.) Accordingly, a POSA would know that “Depotrex” as referenced in Comer refers to PLGA/naltrexone microcapsules used for depot injection as described in Nuwayser.

Comer’s depot formulation was injected into the buttocks of the patients using an 18-gauge needle—*i.e.*, parenteral administration. (Ex. E at 354.) Comer determined that this 384 mg dose of depot naltrexone antagonized heroin-induced subjective ratings for five weeks and plasma levels remained above the therapeutic level of 1 ng/ml for approximately four weeks. (*Id.* at 351.) “These results suggest that this depot formulation of naltrexone provides a safe, effective, long-lasting antagonism of the effects of heroin.” (*Id.*; Ex. H at ¶ 88.)

Thus, Comer teaches the method of claim 1—treating patients in need of naltrexone (heroin dependent patients) by parenterally administering (depot injection into the buttocks) a long-acting (1 ng/ml blood levels for four weeks) formulation of about 310 mg to about 480 mg (384 mg) and PLGA (evidenced by Nuwayser). (Ex. H at ¶ 89.) The only remaining element of the claim is the observed AUC when compared to a 50 mg/day oral dose.

3. “wherein the serum AUC of naltrexone is about three times greater than that achieved by 50 mg/day oral administration”

To establish inherent anticipation, the missing descriptive matter must *necessarily* be present in the thing described in the reference. *Continental Can Co. USA, Inc. v. Monsanto Co.* (948 F.2d 1264, 1268 (Fed. Cir. 1991), quoting *In re Oelrich* (666 F.2d 578, 581) (C.C.P.A. 1981). That is exactly the case with this claim element.

The law does not permit Patent Owners to extend their monopoly by merely claiming an inherent characteristic of a known, and previously disclosed formulation and method of administering that formulation. The situation in the '499 Patent is precisely why the inherency doctrine exists: “one of the principles underlying the doctrine of inherent anticipation is to ensure that the public remains free to make, use or sell prior art compositions or processes, regardless of whether or not they understand their complete makeup or the underlying scientific principles which

allow them to operate.” *SmithKline Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331, 1345-46 (Fed. Cir. 2005) (quotation and alteration omitted)

The AUC and the AUC differential are nothing more than *consequences* of performing the claimed steps—steps that were known—and cannot confer patentability. *See In re Kao*, 639 F.3d 1057, 1070 (Fed. Cir. 2011) (a pharmacokinetic property “adds nothing of patentable consequence” when claimed as a limitation); *see also Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1380 (Fed. Cir. 2001) (“Newly discovered results of known processes directed to the same purpose are not patentable because such results are inherent.”). The inherent anticipation doctrine has been repeatedly emphasized by the Federal Circuit, where the Court consistently holds that the discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, *does not render the old composition patentably new to the discoverer*. *See, e.g., Atlas Powder Co. v. Ireco, Inc.*, 190 F.3d 1347 (Fed. Cir. 1999) (emphasis added).

The result of administering the prior art formulation at the prior art dose necessarily results in the claimed pharmacokinetic property where “the serum AUC of naltrexone is about three times greater than that achieved by 50 mg/day oral administration.” As evidence of the inherency of the claims, the plot of Figure 1 of Comer discloses an AUC that is about three times greater than that achieved by 50

mg/day oral administration to the same extent as the '499 Patent. (Ex. H at ¶¶ 67-74, 81, 89.) This differential results from comparing the AUC of Comer to the oral data presented in Tice or the Ehrich Declaration, the same oral data used by Alkermes when making its comparison. (*Id.*) Thus, Comer's AUC differential over 50 mg/day oral dosing is about 3, indeed about 3.3.

Moreover, during an appeal to the Board filed in the '499 Patent's grandchild, Application No. 13/871,534 (now abandoned), Alkermes admitted that "the pharmacokinetic profile of naltrexone long acting microspheres is *dependent on the dose and formulation* and is simply not inherent to any dose of any PLGA microsphere containing naltrexone", and that "[t]he Examiner appears to ignore the fact that the result (superior efficacy and pharmacokinetic profile) is dose dependent...." (Ex. Z at 6-7.) The dose of Comer is 384 mg, which is essentially the same dose (about 380 mg) as that given in the clinical study reported in the '499 Patent and the Ehrich Declaration, and upon which Alkermes' relied for their observation of alleged unexpected result. (Ex. A at 1:30-40, 8:32-4, 17:49-62.). Further, Comer uses the same formulation with PLGA as described in the claims. Since the doses and formulations are the same and Alkermes has admitted that AUC is dose and formulation dependent, Comer must also have the claimed AUC differential if compared to the same oral dosing data. (Ex. H at ¶¶ 81, 89.)

The addition of a mathematical calculation to the claim does not make the

prior art any less anticipatory nor does it make a prior art method and formulation patentable again. The *Pernix Ireland Pain v. Alvogen Malta Operations*, case is instructive to the facts here. In *Pernix*, the Court found that the claim elements directed to pharmacokinetic limitations were inherently anticipated, even when those claim elements required a comparison and differential between the AUC of subjects suffering from mild hepatic impairment and subjects not suffering from renal or hepatic impairment. *Pernix Ir. Pain DAC v. Alvogen Malta Operations Ltd.*, 323 F. Supp. 3d 566, 605-7 (D. Del. 2018). The Court flatly rejected Patent Owner's arguments that the claims required a particular differential and that the prior art did not disclose that differential: "[t]he Court sees no reason why a pharmacokinetic parameter stated in relative numbers is any less inherent and necessarily present than such a parameter stated in absolute numbers." (*Id.* at 590.) To extend patent protection, the "inventors" of the '499 Patent simply ran a routine clinical trial using a known drug and known method to document an inherent property of the drug. They then claimed the expected and unsurprising results.

Comer's release for a month anticipates claim 3, requiring at least two weeks of naltrexone release, and claim 4, requiring release for four weeks. Claim 5 is anticipated as well. The AUC differential resulting from the comparison of Comer to Tice or the Ehrich Declaration, as just discussed, shows a differential of about three, indeed about 3.3. (Ex. H at ¶¶ 81, 89, 91.)

Finally, claim 12 requires that the parenteral administration be an injection. As noted in connection with claim 1, Comer teaches injection into the buttocks, so claim 12 is anticipated. (Ex. E at 354; Ex. H at ¶ 94.)

B. SNQ Ground 2: Claims 1, 3-5, and 10-12 are anticipated by Vivitrex Pilot Study

Challenged claims 1, 3-5, and 10-12 are also anticipated by the Vivitrex Pilot Study. The challenged claims are not entitled to claim priority to U.S. Provisional Application No. 60/654,542 (and at best have an effective filing date of the non-provisional filing of March 17, 2005), because the provisional application does not support and enable the challenged claims.

To claim priority based on an earlier application, “each previous application in the chain must comply with the written description requirement of 35 U.S.C. § 112(a),” *L.A. Biomedical Rsch. Int. v. Eli Lilly & Co.*, 849 F.3d 1049, 1057 (Fed. Cir. 2017), and must “enable an ordinarily skilled artisan to practice the invention claimed” in the later application, *Allgenesis Biotherapeutics Inc. v. Cloudbreak Therapeutics, LLC*, IPR2020-01438, Paper 7 at 23 (PTAB Feb. 18, 2021) (quoting *Amgen Inc. v. Sanofi*, 872 F.3d 1367, 1380 (Fed. Cir. 2017)). “Patent claims are awarded priority on a claim-by-claim basis based on the disclosure in the priority applications.” *Lucent Techs., Inc. v. Gateway, Inc.*, 543 F.3d 710, 718 (Fed. Cir. 2008).

The provisional application does not support the challenged claims because it does not contain critical information necessary for a POSA to make and use the claimed invention without undue experimentation. The Board previously found “the ’499 patent does not provide a value (or underlying data) for the serum AUC of the disclosed long-acting formulation of naltrexone, or a value (or underlying data) for the serum AUC of the 50 mg/day oral formulation.” (Ex. K at 9.) The underlying provisional application lacks these data as well.

In its prior Institution Decision, the Board interpreted the critical AUC claim limitation essentially incorporating data presented in the Ehrich declaration, filed five years after the provisional application was filed. (Ex. K at 9.) But these data, which are otherwise unsupported, have no basis in the application text and *de facto* constitute added subject matter wholly absent from the provisional application (and the ’499 Patent as of its filing date). The Ehrich declaration cannot be used to fill in the gaps of an insufficient written description in the application because that declaration is not part of the application. *Allergan, Inc. v. Sandoz Inc.*, 796 F.3d 1293, 1309 (Fed. Cir. 2015) (explaining that “[t]he written description requirement requires possession as shown in the specification, not as shown by prior experimental work” where that data is not part of the specification). Without these data, the challenged claims are unsupported and would never have been allowed (Ex. U at 3-5.)

These data are also critical for a POSA to determine whether a particular “long acting formulation” of “about 310 mg to about 480 mg of naltrexone and a biocompatible polymer” would produce a “serum AUC of naltrexone is about three times greater than that achieved by 50 mg/day oral administration.” Indeed, comparing the AUC data of the “long-acting formulation” in the Ehrich declaration against other publicly available data for 50 mg/day oral dosing results in an AUC differential which could be as low as 2.1 or as high as 5.3 times that of oral dosing. (Ex. H at ¶¶ 82-83.) Without identifying the proper benchmark 50 mg/day comparator data, which Alkermes only provided much later, a POSA would have been unable to “make and use” the subject matter recited in the challenged claims. In fact, as noted above, without that comparator data, the claims are indefinite because there are different sources of data that could be used as the 50 mg/day oral dosing data, and depending on which data is selected, the AUC differential calculation would be different. In other words, the same method could in one instance infringe, and in another instance not infringe, simply based on which data was used in the calculation. *Teva*, 789 F.3d at 1341-45; *see also*, *Otsuka*, 151 F.Supp.3d at 544-549 (D.N.J. 2015), (aff’d, Fed. Cir. 2017).

Likewise, the provisional application does not provide full written description support for the challenged claims, because it does not describe the invention in sufficient detail such that a POSA would reasonably conclude Alkermes had

possession of the *full scope* of the challenged claims. As explained above, the provisional application does not include the specific AUC data required to arrive at a “serum AUC of naltrexone is about three times greater than that achieved by 50 mg/day oral administration.” Without these data, a POSA could arrive at an AUC differential which could be as low as 2.1 or as high as 5.3 times that of oral dosing and would thus be unable to conclude one way or another whether Alkermes had possession of the challenged claims. Because the ’499 Patent is not entitled to the priority date of the provisional application, the Vivitrex Pilot Study is prior art. Additionally, the data presented in the Ehrich declaration related only to a 190 mg dose (showing “approximately 2-fold higher AUC”) and a 380 mg dose (showing “about 3.3 times greater” AUC). Nowhere in the provisional application, nonprovisional application, or prosecution record did Patent Owner provide data demonstrating possession of “serum AUC ... about three times greater” than 50 mg/day across the entire claimed range, *i.e.* from “about 310 mg to about 480 mg of naltrexone.”

1. Claim 1

Claim 1 is anticipated by the Vivitrex Pilot Study. The pilot study provides a method for treating an individual in need of naltrexone, in this case an individual suffering from alcoholism. (Ex. G at Abstract.) During the study, as indicated above, Vivitrex was administered intramuscularly, which is a type of parenteral

administration. (*Id.*; Ex. H at ¶ 89.) The dose of naltrexone administered was 400 mg, i.e., between “about 310 mg to about 480 mg.” (Ex. G at Abstract.) The formulation included a biocompatible polymer which is a “polylactide-co-glycolide polymer.” (*Id.* at 1357.)

Furthermore, as discussed above at Section X(B), the AUC and the AUC differential is an inherent property that depends on the dose and formulation. For the same reasons as discussed in SNQ Ground 1, the administration of Vivitrex according to the Pilot Study would have resulted in the claimed AUC (Ex H at ¶¶ 78-81.) In fact, during prosecution of a continuation application (U.S. Patent Application No. 13/871,534), Alkermes confirmed the AUC data in the Ehrich declaration was derived from administration of “Vivitrex® microspheres to human patients” containing 380 mg naltrexone. (Ex. Z at 19.) The administration to human patients of a Vivitrex formulation containing 400 mg naltrexone during the Pilot Study is well within the claimed range and thus would have similarly produced serum AUC that, when compared to the 50 mg/day administration data from the Ehrich declaration, was also about three times greater. The Vivitrex Pilot Study therefore anticipates claim 1.

2. Dependent Claims 3-5 and 10-12

Claim 3, requiring release of naltrexone “for a period of at least two weeks,” and claim 4, requiring release “for a period of about four weeks” are also anticipated.

The Vivitrex Pilot Study reported “[p]armacokinetic analyses demonstrated that therapeutic levels of naltrexone were delivered by the extended-release injectable formulation throughout each 1-month treatment cycle.” (Ex. G at 1360.)

Claim 5 is anticipated as well. The Vivitrex Pilot Study administered a dose “of about 380 mg of naltrexone” and, as described above, would have necessarily produced a serum AUC differential of at least 3.3.

Claim 10 requires the patient is alcohol dependent. The patients in the Vivitrex Pilot study were alcohol dependent. (Ex. G at Abstract.) Claim 10 is therefore anticipated. (Ex H at ¶¶ 78-81.)

Claim 11 requires that the patient not receive an “initial” dose of naltrexone orally. In the Vivitrex Pilot, patients did not get an initial oral naltrexone. (Ex. G at 1357) (“On day 0, enrolled patients were administered the first dose of study drug. Subsequent doses were administered on days 28, 56, and 84.”) Therefore, claim 11 is anticipated.

Finally, claim 12 requires that the parenteral administration be an injection. As noted in connection with claim 1, the Vivitrex Pilot Study administered via intramuscular injection. (Ex. G at Abstract.)

**C. SNQ Ground 3: The Challenged Claims Are Obvious Over
Comer in View of Nuwayser, Rubio, and Wright**

The challenged claims are obvious over Comer in view of Nuwayser as those

references are described in SNQ Ground 1.

1. Claim 1

As described in detail in SNQ Ground 1, Comer discloses the method of claim 1—treating patients in need of naltrexone (heroin dependent patients) by parenterally administering (depot injection into the buttocks) a long acting (1 ng/ml blood levels for four weeks) formulation of about 310 mg to about 480 mg (384 mg) and a biocompatible PLGA polymer (Depotrex). (Ex. H at ¶¶ 87-89, 100-102.)

To the extent that any of the elements of claim 1 are not found explicitly or inherently in Comer, they would have certainly been obvious in view of Nuwayser. For example, if one did not accept that Nuwayser provided the information about Depotrex taught by Comer to a POSA as explained in SNQ Ground 1, a POSA would nonetheless be motivated to use the Nuwayser naltrexone formulation in the method taught by Comer with a reasonable expectation of success. Assuming Comer does not specifically describe the specific naltrexone formulation that should be used, a POSA would naturally seek out acceptable formulations to achieve the effect described by Comer. (Ex. H at ¶ 102.) Comer teaches a method of treating heroin addicts by using 384 mg naltrexone in parentally injectable naltrexone-containing microcapsules. (Ex. E at 351, 354, 358-359, Fig. 1.) Arguably, except for the specific dose, Nuwayser teaches the same. (Ex. F at 19:4-25; Ex. H at ¶¶ 87-90, 101-102.) And both provide data on the release profile of their formulations, which a POSA

would immediately recognize to be the same, or nearly so. (Ex. E at Fig. 1; Ex. F at Fig. 7; Ex. H at ¶¶ 75-77, 102.)

A POSA would therefore reasonably expect that using sufficient PLGA microparticles produced in accordance with Nuwayser to provide 384 mg dose of naltrexone called for in Comer would achieve the results of Comer, *i.e.*, a 28-day release of a therapeutic dose of naltrexone having a similar release profile and AUC. (Ex. H at ¶ 98.) And, as AUC is dose dependent and Comer teaches giving the claimed dose, the claimed AUC differential, or one rendering it obvious, would reasonably be expected if the same oral data used by Alkermes was used to calculate the differential. (Ex. H at ¶ 102.) Indeed, when the AUCs of Comer and Nuwayser are compared to the oral data in Tice and in the Ehrich Declaration, the AUC differential is about three, indeed about 3.3 (Ex. H at ¶¶ 81, 89, 102-103, 107.)

Given that the data provided in the AUC plots of Comer and Nuwayser are indistinguishable (Ex. H at ¶¶ 75-77), and that both stated that they provided therapeutic doses for about a month, a POSA would also have a reasonable expectation that their combined teachings would be successful. (Ex. E at 351, 359 (“These results suggest that this depot formulation of naltrexone provides a safe, effective long-lasting antagonism of the effects of heroin.”); Ex. F at 19:23-25 (“This formulation delivered a therapeutic level of naltrexone in six heroin addicts for a period of 30 days (*see* FIG. 7).”); Ex. H at ¶¶ 101-102, 106-107.)

Even if the claimed AUC differential did not result from this combination, the claims would still be obvious because the claimed formulation and method were known in view of Comer and Nuwayser, and the resulting serum concentration is merely the consequence of administering the known formulation in the known method. *Santarus, Inc. v. Par Pharm, Inc.*, 694 F.3d 1344, 1354 (Fed. Cir. 2012) (“[A]n obvious formulation cannot become nonobvious simply by administering it to a patient and claiming the resulting serum concentrations.”), *see also id.* (“To hold otherwise would allow any formulation—no matter how obvious—to become patentable merely by testing and claiming an inherent property.”).

Moreover, this limitation should be given no patentable weight. A newly discovered fact or property of does not remove a method from the domain of prior art. *See, e.g., Atlas Powder Co.*, 190 F.3d 1342, 1347 (Fed. Cir. 1999) (“[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art’s functioning, does not render the old composition patentably new to the discoverer.”). In this case, there is no doubt that each of the positive steps of the method recited in claim 1 of the ’499 Patent is shown in Comer. Alkermes’s “discovery” of one of the consequences of following each of the positive steps—i.e., the claimed AUC differential—is nothing more than non-functional, descriptive material that does not alter any of affirmatively recited process steps in the claim. *In re Oelrich*, 666 F.2d 578, 581 (C.C.P.A. 1981)

("[M]ere recitation of a newly discovered function or property, inherently possessed by things in the prior art, does not distinguish a claim drawn to those things from the prior art."); *cf. Ansonia Brass & Copper Co. v. Elec. Supply Co.*, 144 U.S. 11, (1892) ("[N]othing is better settled in this court than that the application of an old process to a new and analogous purpose does not involve invention, even if the new result had not before been contemplated.").

Even if the AUC differential limitation entitled to *some* weight, at best that weight should be *de minimis*. A POSA would realize that the AUC and AUC differential between a depot injection and oral dosing of naltrexone would not be expected to have a meaningful impact on efficacy. (Ex. H at ¶¶ 16, 60-62, 64.) So long as therapeutic blood levels were maintained, which was known in the art to result from oral dosing and depot injections, the treatment should be equally effective no matter how much higher the blood concentration, *i.e.*, the AUC (assuming compliant use) (Ex. H at ¶¶ 44, 52, 54, 60.)

Nothing in the specification would suggest to a POSA that using a naltrexone depot injection (whether it is that described by the '499 Patent, in Comer, or Nuwayser) would provide meaningfully different therapeutic effects than oral dosing 50 mg/day. (Ex. H at ¶¶ 16, 61-62.) A depot injection might provide better compliance, but that was known. (Ex. E at 351-352; Ex. H at ¶ 54.) Indeed, when distinguishing oral dosing and other depot injections during prosecution, Alkermes

noted that Tice resulted in an AUC that was roughly the same as oral dosing—not three times that level as claimed. (Ex. D at 4.) Alkermes did not argue, however, that either was less effective. (Ex. H at ¶¶ 16, 61-62.)

Moreover, a POSA would discount any AUC differential because it did not result from a comparison made to the closest prior art. Here the closest prior art is not oral dosing or Tice, as the Examiner suggested. (Ex. H at ¶¶ 24, 63-65.) Instead, a POSA would look to Comer and Nuwayser, alone or in combination, both of which involved administering about 380 mg naltrexone in a PGLA-containing formulation as once-a-month depot injections. (Ex. H at ¶¶ 101-107.) Since the dose, formulation, and manner of administration were exactly the same as that claimed, and the pharmacokinetic plots of each can be superimposed, a POSA would understand that the AUC and differential should all be the same or not patentably different. (Ex. H at ¶¶ 64-77, 81, 89, 96, 102-103.)

Further, a POSA would be concerned that the AUC comparisons made in the '499 Patent are hypothetical. Unlike direct comparisons to one-month depot injections, this comparison is based on the use of oral AUC data obtained for a single day. To make a comparison, one must artificially divide or average the one-month data or assume that the one-day's data is consistent and multiply it by 28 days. (Ex. H at ¶ 65.) Accordingly, a POSA would not consider any difference in AUC differential to be significant for all the reasons discussed herein, especially

considering the sensitivity of the oral data used. (Ex. H at ¶¶ 81-86.)

2. Dependent Claims 2-13

Turning to the dependent claims, claim 2 requires that treatment occur every 4 weeks and last for at least 24 weeks and that there be no prior oral dose of naltrexone. As to the former, treating patients every 4 weeks for 24 weeks or more is obvious. Comer teaches that naltrexone had already been used for “chronic administration of over 1 year.” (Ex. E at 351.) Moreover, Rubio teaches that treatment protocols of 12 months in alcoholics were known. (Ex. W at 419-420.) As to the latter limitation, Comer contemplated treating with the depot injection without a prior oral dose of naltrexone. (Ex. E at 359 (“In a treatment setting where oral naltrexone may not be given prior to depot naltrexone”).) Similarly, Nuwayser has no disclosure of providing its patients with oral doses of naltrexone. Claim 2 is therefore obvious. (Ex. H at ¶ 108.)

Claim 3 requires at least two weeks of naltrexone release, while claim 4 requires about four weeks. Four-week release is taught by both Comer and Nuwayser as noted in connection with claim 1 above. Accordingly, these claims are obvious as well. (Ex. H at ¶ 109.)

Claim 5 requires that the AUC be about 3.3 times that of 50 mg/day oral dosing. Comer and Nuwayser both disclose this. (Ex. H at ¶¶ 81, 89, 109.) Moreover, as just discussed, any difference in AUC differential would not carry patentable

weight, as the difference is not meaningful in terms of therapeutic efficacy, the differential was not determined by a comparison to the closest art, and the differential is subject to mathematical manipulation.

Claim 6 requires that the treatment last at least 24 weeks. This is obvious for the reasons described in connection with claim 2, which includes the same limitation. (Ex. H at ¶ 110.)

Claims 7-9 require a second dose be given seven days or more after the first one is given, and that the subsequent dose be substantially similar to (claim 8) or the same as (claim 9) to the first dose. This protocol would be obvious to a POSA. Since Comer and Nuwayser both teach four-week dosing, a POSA would not consider a second dose earlier than seven days. (Ex. H at ¶ 111.) Moreover, if a single 7, 14, or even 30-day period were all that was needed for alcohol or opioid treatment, the very compliance problem that drives the reasoning for a depot injection would not be as compelling. A POSA would expect that more than one four-week dose would be needed. And there is no reason to use different formulations than the one already established as successful. (Ex. H at ¶ 111.)

Claim 10 specifies that the patient is alcohol dependent. Comer acknowledged that naltrexone had already been established to be safe and effective in alcoholics. (Ex. E at 352.) Rubio teaches treating alcoholics as well. (Ex. W at 419-420; Ex. H at ¶ 112.) Because naltrexone was a well-established treatment for alcoholism as of

the priority date of the challenged claims, it would have been obvious based on the prior art to use the formulation in Comer to treat alcohol dependent patients.

Claim 11 requires that the patient not receive an “initial” dose of naltrexone orally. In Comer, patients did receive oral naltrexone, but the oral dosing in Comer was not a treatment dose, as it was given to ensure study participants were “willing and able to tolerate its effects.” (Ex. E at 353.) Comer expressly contemplates that “[i]n a *treatment* setting ... oral naltrexone may not be given prior to depot naltrexone.” (Ex. E at 359, emphasis added.) Additionally, there is no oral dosing suggested in Nuwayser. (Ex. H at ¶ 113.) As a result, it would have been obvious to omit an initial oral treatment dose of naltrexone and Claim 11 is therefore obvious.

Claim 12 requires that the parenteral administration be an injection. Comer teaches injection into the buttocks. (Ex. E at 354.) Nuwayser teaches subcutaneous injection. (Ex. F at Fig. 7.) Claim 12 is therefore obvious. (Ex. H at ¶ 113.)

Claim 13 requires that the naltrexone be present in the amount of about 35% by weight of the formulation. Nuwayser exemplifies a formulation that includes naltrexone in the amount of 54.4% by weight. (Ex. F at 19:22-23.) It was well-known that drug loading could be in the range of 30-75% by weight of the formulation. (Ex. N at 7:63-8:1; Ex. H at ¶ 114.)

D. SNQ Ground 4: The Challenged Claims Are Obvious Over the Vivitrex Pilot Study In View Of Comer, Rubio, And Wright

The challenged claims are obvious based on the Vivitrex Pilot Study, in view of Comer as those references are described in SNQ Grounds 1 and 2.

1. Claim 1

The Vivitrex Pilot Study discloses the method of claim 1—treating patients in need of naltrexone (“alcohol-dependent patients”) by parenterally administering (“gluteal injection”) a long acting formulation (“extended release” formulation dosed “every 28 days over 4 months”) of about 310 mg to about 480 mg (“400 mg”) and a biocompatible PLGA polymer (microspheres composed of “naltrexone incorporated into a matrix of polylactide-co-glycolide”).

Although the 400 mg dose in the Vivitrex Pilot Study is well within the claimed range, and would inherently have produced the claimed AUC differential, it would also have been obvious to adjust the dose in the Vivitrex Pilot Study formulation to include another dose within the claimed range, for example 384 mg of naltrexone used in Comer. A POSA would have been motivated to make this adjustment with a reasonable expectation of success because Comer reports a 384 mg extended-release dose comprising PLGA microspheres produced therapeutic naltrexone blood plasma levels above 1 ng/ml for approximately 4 weeks after administration (Ex. E at Abstract; Ex. H at ¶¶ 54-55.) A formulation of 384 mg of

naltrexone in the Vivitrex polymer delivery system would have produced essentially the same AUC differential as a 380 mg dose in the same system. (Ex. H at ¶¶ 81, 89.)⁶

It also would have been obvious to adjust the polymer formulation to account for the slight variation in naltrexone dose (400 mg vs. 384 mg) to slightly adjust the AUC. As Patent Owner argued during prosecution of '499 Patent, "it is well within the ability of the skilled person to, for example, adjust the various components of the polymer delivery systems ... to determine the effect on the desired feature. An algorithm for calculation of each of the components can then be developed for each class of biocompatible polymer and used to screen one or more types of compatible biopolymers using standard techniques to determine which are capable of meeting the AUC." (Ex. O, U.S. Application No. 11/083,167, at 9-10.) Accordingly, claim 1 is obvious.

2. Dependent Claims 2-13

Claim 2 requires that treatment occur every 4 weeks and last for at least 24 weeks and that there be no prior oral dose of naltrexone. As to the former, treating patients every 4 weeks for 24 weeks or more is obvious. The Vivitrex Pilot Study

⁶ As with Ground 3, even if the claimed AUC differential did not result from this combination, the claims would still be obvious because this limitation should be given no patentable weight.

treated patients every 4 weeks for 16 weeks, and it would have been obvious to extend the treatment protocol. Comer teaches that naltrexone had already been used in the prior art for “chronic administration of over 1 year.” (Ex. E at 351.) Moreover, Rubio teaches that treatment protocols of 12 months in alcoholics were known. (Ex. W at 419-420.)

As to the latter limitation, the Vivitrex Pilot Study excluded patients treated with naltrexone 10 days or less before screening. (Ex. G at 1357.) It would have been obvious to exclude patients who had ever received naltrexone, as Comer contemplated treating with the depot injection without a prior oral dose of naltrexone. (Ex. E at 359 (“In a treatment setting where oral naltrexone may not be given prior to depot naltrexone”).) Claim 2 is therefore obvious. (Ex. H at ¶ 93.)

Claim 3 requires at least two weeks of naltrexone release, while claim 4 requires about four weeks. Four-week release is taught by the Vivitrex Pilot Study and Comer as noted in connection with claim 1 above. Accordingly, these claims are obvious as well.

Claim 5 requires that the AUC be about 3.3 times that of 50 mg/day oral dosing. As discussed above, this feature is either inherent or else it would have been obvious to adjust the dose in the Vivitrex Pilot Study to the 384 mg dose disclosed in Comer. The 384 mg extended release dose in Comer discloses an AUC about 3.3 times that of 50 mg/day oral dosing. (Ex. H at ¶¶ 75-77, 81, 89, 98.) Moreover, as

discussed previously, any difference in AUC differential should not carry patentable weight, as the difference is not meaningful in terms of therapeutic efficacy, the differential was not determined by a comparison to the closest art, and the differential is subject to mathematical manipulation.

Claim 6 requires that the treatment last at least 24 weeks. This is obvious for the reasons described in connection with claim 2, which includes the same limitation. (Ex. H at ¶ 110.)

Claims 7-9 require a second dose be given seven days or more after the first one is given, and that the subsequent dose be substantially similar to (claim 8) or the same as (claim 9) to the first dose. The Vivitrex Pilot Study administered four identical doses (400 mg) on days 0, 28, 56, and 84, which meets this claim limitation. Additionally, given the Vivitrex Pilot Study and Comer each teach four-week dosing, a POSA would not consider a second dose earlier than seven days. (Ex. H at ¶ 111.) As noted above, a POSA would expect that more than one four-week dose would be needed, and there is no reason to use different formulations than the one already established as successful. (Ex. H at ¶ 111.)

Claim 10 specifies that the patient is alcohol dependent. The Vivitrex Pilot Study treated “alcohol-dependent patients.” (Ex. G at Abstract.) Additionally, Comer acknowledged that naltrexone had already been established to be safe and effective in alcoholics. (Ex. E at 352.) Rubio teaches treating alcoholics as well. (Ex.

W at 419-420; Ex. H at ¶ 112.)

Claim 11 requires that the patient not receive an “initial” dose of naltrexone orally. Patients in the Vivitrex Pilot Study were not administered an initial oral dose of naltrexone. (Ex. G at 1357.) Claim 11 is therefore obvious.

Claim 12 requires that the parenteral administration be an injection. The formulation in the Vivitrex Pilot Study was “as a gluteal injection.” (Ex. G at 1357.) Comer also teaches injection into the buttocks. (Ex. E at 354.) Claim 12 is therefore obvious. (Ex. H at ¶ 113.)

Claim 13 requires that the naltrexone be present in the amount of about 35% by weight of the formulation. Vivitrex does not provide a weight percent of naltrexone in its formulation but notes the name of its extended release technology is “Medisorb®.” Example 3 of Wright discloses a naltrexone formulation containing Patent Owner’s “Medisorb®” polymer in which naltrexone drug loading ranged from 30%-70%. (Ex. N at 7:63-8:1; Ex. H at ¶ 114.) A POSA with knowledge of the Vivitrex Pilot Study would have looked to Wright to understand the potential range of drug loading and would have been motivated to combine the Vivitrex Pilot Study with Wright with a reasonable expectation of success. To the extent the Vivitrex Pilot Study does not inherently disclose this limitation, it would have been obvious to adapt the naltrexone drug loading within the 30-75% range disclosed by Wright. (Ex. H at ¶¶ 50, 114, 125, 143.)

XI. SECONDARY CONSIDERATIONS

It is Alkermes' burden to establish secondary indicia of nonobviousness, if any. Alkermes did not offer any evidence during prosecution of the '499 Patent of commercial success, copying, long-felt but unmet need, skepticism, and industry acclaim. And as discussed previously, Alkermes will likely be unsuccessful in proving the existence of unexpected and superior results, or that there is a nexus between any secondary indicia, such as commercial success, and the claims of the '499 Patent.

Although objective indicia of non-obviousness must be considered, they do not necessarily control the obviousness conclusion. *Newell Cos., Inc. v. Kenney Mfg. Co.*, 864 F.2d 757, 768 (Fed. Cir. 1988). In fact, a strong case of obviousness, like Requester has made here, cannot be overcome by objective evidence of non-obviousness. *See Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1372 (Fed. Cir. 2007); *Hoffmann-La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326, 1334 (Fed. Cir. 2014). Especially "where a claimed invention represents no more than the predictable use of prior art elements according to established functions, as here, evidence of secondary indicia are frequently deemed inadequate to establish non-obviousness." *Ohio Willow Wood Co. v. Alps South, LLC*, 735 F.3d 1333, 1344 (Fed. Cir. 2013).

Even if, for sake of argument, one accepted that about three times the claimed AUC difference was unexpected, this AUC differential varies based on the

comparator data, making it subject to manipulation or obfuscation. There is nothing on the record to establish that the claimed AUC differential is an unexpected superior result. *In re Soni*, 54 F.3d 746, 750-51 (Fed. Cir. 1995) (“Mere improvement in properties does not always suffice to show unexpected results.”)

In this instance, the AUC “discovery” is an observation of a property of certain long-acting naltrexone dosage forms, but ultimately does not possess real significance. *See Galderma Labs., LP v. Tolmar, Inc.*, 737 F.3d 731, 739 (Fed. Cir. 2013) (Unexpected results that are probative of non-obviousness are those that are “different in kind and not merely in degree from the results of the prior art.”). *See In re Harris*, 409 F.3d 1339, 1344 (Fed. Cir. 2005) (affirming obviousness rejection where 32–43% increase in stress rupture life was not a “difference in kind”).

Even if the AUC did increase unexpectedly, Alkermes’ showings should be given minimal weight given the complete lack of any meaningful evidence of superiority—not to mention the lack of any data or clarity as to what data to use to demonstrate superiority. It should not overcome the strong showing of anticipation and/or obviousness discussed above.

Moreover, to prove commercial success, Alkermes must establish that any commercial success it enjoyed was based on patentable features—features of its invention that were not disclosed in the prior art. *See Asyst Techs., Inc. v. Emtrak, Inc.*, 544 F.3d 1310, 1316 (Fed. Cir. 2008); *see also J.T. Eaton & Co. v. Atl. Paste*

& *Glue Co.*, 106 F.3d 1563, 1571 (Fed. Cir. 1997). The commercial success of Alkermes' Vivitrol product is meaningless unless it can be attributed to the claimed features of the '499 Patent. Here, all of the claimed features, even the purported AUC differential, were known or obvious. More importantly, Vivitrol is prescribed because it provides an effective treatment, not because it provides a higher AUC than some other treatment.

Finally, as previously recognized by the Federal Circuit, market entry here has been precluded by a complex regulatory scheme. Accordingly, any inference of nonobvious based on commercial success is "weak." *Merck & Co. v. Teva Pharms.*, 395 F.3d 1364, at 1377 (Fed. Cir. 2005). There are also significant issues as to the commensurateness of any showing. Alkermes' showing, at best, was for a 380 mg dose. It has not provided sufficient evidence to support the claimed dose range of 310-480 mg despite acknowledging dose-dependence.

XII. CONCLUSION

For the foregoing reasons, the references cited above raise substantial new questions of patentability with respect to claims 1-13 of the '499 patent. Therefore, Requester respectfully asks that this request for ex parte reexamination be granted and that claims 1-13 of the '499 patent be rejected.

Request for *Ex Parte* Reexamination of
U.S. Patent No. 7,919,499

Respectfully submitted,

December 16, 2024

/Shannon M. Lentz/

Shannon M. Lentz

Registration No. 65,382

CROWELL & MORING LLP
Intellectual Property Group
P.O. Box 14300
Washington, DC 20044-4300
Telephone No.: (202) 624-2500
Facsimile No.: (202) 628-8844
SML:ALB:hjk

CERTIFICATE OF SERVICE

I hereby certify, pursuant to 37 C.F.R. § 1.510(b)(5), that a complete copy of the attached REQUEST FOR EX PARTE REEXAMINATION OF U.S. PATENT NO. 7,919,499, including all Exhibits, was served on December 16, 2024, via Federal Express upon the Patent Owner by serving the correspondence address of record with the USPTO as follows:

Elmore Patent Law Group
484 Groton Road
Westford, MA 01886

Respectfully submitted,

December 16, 2024

/Shannon M. Lentz/
Shannon M. Lentz
Registration No. 65,382