

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

APOTEX INC.
Petitioners

v.

ALKERMES PHARMA IRELAND LIMITED
Patent Owner

Case No. IPR2025-00514
Patent 7,919,499

**PETITION FOR *INTER PARTES* REVIEW
OF U.S. PATENT NO. 7,919,499**

TABLE OF CONTENTS

	<u>Page</u>
I. INTRODUCTION	1
II. MANDATORY NOTICES PURSUANT TO 37 C.F.R. §42.8(a)(1)	3
A. Real Parties-In-Interest.....	3
B. Identification of Related Matters Under 37 C.F.R. §42.8(b)(2)	3
C. Lead and Backup Counsel.....	5
D. Service Information Under 37 C.F.R. §42.8(b)(4).....	6
III. FEES	6
IV. REQUIREMENTS UNDER 37 C.F.R. §42.104.....	6
A. Grounds for Standing	6
B. Identification of Challenges and Precise Relief Requested	6
C. Prior Art Qualification of Asserted References	7
V. BACKGROUND	8
A. The '499 Patent	8
B. The '499 Patent Examination History.....	10
C. The Terminated '943 IPR.....	12
D. Summary of the Applied Prior Art.....	14
1. Comer (EX1004).....	14
2. Nuwayser (EX1005)	17
3. Rubio (EX1006).....	18
4. Wright (EX1007)	19
E. Person of Ordinary Skill in the Art (“POSITA”).....	20

VI.	CLAIM CONSTRUCTION	20
A.	“the step of parenterally administering a long acting formulation comprising about 310 mg to about 480 mg of naltrexone”	21
B.	“the serum AUC of naltrexone ... than that achieved by 50 mg/day oral administration”	23
C.	“about three”	25
D.	“five or more days”	26
E.	“initial oral dose”	26
F.	“about 35% by weight”	27
VII.	PETITIONER HAS A REASONABLE LIKELIHOOD OF PREVAILING	27
A.	Ground 1: Claims 1, 3-5, and 12 Are Anticipated by Comer as evidenced by Nuwayser	28
1.	Claim 1 (Preamble): A method for treating an individual in need of naltrexone comprising the step of.....	28
a.	[1.1]: parenterally administering a long acting formulation comprising	29
b.	[1.2]: about 310 mg to about 480 mg of naltrexone	32
c.	[1.3]: and a biocompatible polymer to the individual	33
d.	[1.4]: wherein the serum AUC of naltrexone is about three times greater than that achieved by 50 mg/day oral administration	33
e.	[1.5]: and wherein the biocompatible polymer is a polylactide-co-glycolide polymer.....	36
2.	Claim 3: The method of claim 1 wherein the long acting formulation releases naltrexone for a period of at least two weeks.....	36

3.	Claim 4: The method of claim 1 wherein the long acting formulation releases naltrexone for a period of about four weeks.....	37
4.	Claim 5: The method of claim 1 wherein the long acting formulation is administered in a dose of about 380 mg of naltrexone wherein the serum AUC is about 3.3 times greater than that achieved by 50 mg/day oral administration.....	37
5.	Claim 12: The method of claim 1 wherein naltrexone is administered by injection.	38
B.	Ground 2: Claims 1-13 Would Have Been Obvious Over Comer in view of Nuwayser, Rubio, and Wright	38
1.	Claim 1	38
2.	Claim 2	48
3.	Claim 3	49
4.	Claim 4	49
5.	Claim 5	49
6.	Claim 6	49
7.	Claims 7-9	50
8.	Claim 10	51
9.	Claim 11	51
10.	Claim 12	52
11.	Claim 13	52
C.	Ground 3: Claims 1-13 Would Have Been Obvious Over Nuwayser in View of Comer, Rubio, and Wright.....	53
1.	Claim 1 (Preamble)	53
a.	Element [1.1]	54

Petition for *Inter Partes* Review of U.S. Patent No. 7,919,499

b.	Element [1.2]	54
c.	Element [1.3]	57
d.	Element [1.4]	57
e.	Element [1.5]	58
2.	Claim 2	58
3.	Claim 3	58
4.	Claim 4	59
5.	Claim 5	59
6.	Claim 6	59
7.	Claims 7-9	60
8.	Claim 10	60
9.	Claim 11	60
10.	Claim 12	60
11.	Claim 13	61
VIII.	OTHER CONSIDERATIONS	61
A.	Any Purported Secondary Considerations Evidence Does Not Overcome the Strong Evidence of the Obviousness of the Claims	61
B.	The Amneal IPR Does Not Warrant Discretionary Denial Under <i>General Plastic</i>	62
IX.	CONCLUSION	68
APPENDIX A - Naltrexone AUC calculations based on 384 mg IM dose		
APPENDIX B - LIST OF EXHIBITS		
CERTIFICATE OF COMPLIANCE WITH 37 C.F.R. §42.24		
CERTIFICATE OF SERVICE		

TABLE OF AUTHORITIES

Cases	Page(s)
<i>Amneal Pharmaceuticals LLC v. Alkermes Pharma Ireland Limited</i> , IPR2018-00943	<i>passim</i>
<i>Apple Inc. v. Fintiv, Inc.</i> , IPR2020-00019, Paper 11 (PTAB Mar. 20, 2020)	65, 66
<i>Baldwin Graphic Sys., Inc. v. Siebert, Inc.</i> , 512 F.3d 1338 (Fed. Cir. 2008)	21
<i>In re Baxter Travenol Labs.</i> , 952 F.2d 388 (Fed. Cir. 1991)	30
<i>Comcast Cable Commn's, LLC v. Rovi Guides, Inc.</i> , IPR2019-00231, Paper 14 (PTAB May 20, 2019)	66
<i>DISH Network LLC v. Sound View Innovations, LLC</i> , IPR2020-01041, Paper 13 (PTAB Jan 19, 2021)	67
<i>General Plastic Indus. Co., Ltd. v. Canon Kabushiki Kaisha</i> , IPR2016-01357, Paper 19 (PTAB Sept. 6, 2017).....	62, 63, 64, 65
<i>Google LLC v. Multimodal Media LLC</i> , IPR2024-00053, Paper 10 (PTAB Jun. 5, 2024)	65
<i>Inergy Tech., Inc. v. Force Mos Tech., Co., Ltd.</i> , IPR2024-00094, Paper 9 (PTAB May 21, 2024)	66
<i>Puma N. Am., Inc. v. Nike, Inc.</i> , IPR2019-01058, Paper 10 (PTAB Oct. 31, 2019).....	68
<i>Roku, Inc. v. Universal Electronics, Inc.</i> , IPR2019-01615 (PTAB April 17, 2020)	67
<i>Santarus, Inc. v. Par Pharm., Inc.</i> , 694 F.3d 1344 (Fed. Cir. 2012)	2
<i>Trans Ova Genetics, LC v. XY, LLC</i> , IPR2018-00250, Paper 9 (PTAB June 27, 2018)	67

<i>Valve Corp. v. Electronic Scripting Prods., Inc.</i> , IPR2019-00062, Paper 11 (PTAB Apr. 2, 2019)	63, 64
<i>Videndum Prod. Solutions, Inc. v. Rotolight Ltd.</i> , IPR2023-01218, Paper 12 (PTAB Apr. 19, 2024)	64

Statutes

35 U.S.C. §102(b)	7, 8
35 U.S.C. §102(e)	8
35 U.S.C. §103(a)	7
35 U.S.C. §112	22, 25
35 U.S.C. §§311-319	1
35 U.S.C. §314(a)	65
35 U.S.C. §325(d)	67

Rules

37 C.F.R. §1.75(c)	22
37 C.F.R. §1.102(e)	10
37 C.F.R. §1.132	11, 24
37 C.F.R. §42.8(a)(1)	3
37 C.F.R. §42.8(b)(1)	3
37 C.F.R. §42.8(b)(2)	3
37 C.F.R. §42.8(b)(3)	5
37 C.F.R. §42.8(b)(4)	6
37 C.F.R. § 42.10(a)	5

Petition for *Inter Partes* Review of U.S. Patent No. 7,919,499

37 C.F.R. §42.10(b)	6
37 C.F.R. §42.15(a).....	6
37 C.F.R. §42.100 <i>et seq.</i>	1
37 C.F.R. §42.102(a)(2).....	6
37 C.F.R. §42.104	6
37 C.F.R. §42.104(a).....	6
37 C.F.R. §42.104(b)	7
MPEP §2131.01 [I], [II]	30

I. INTRODUCTION

Apotex Inc. (“Petitioner”) respectfully request *inter partes* review for Claims 1-13 (“the Challenged Claims”) of U.S. Patent No. 7,919,499 (“the ’499 Patent”) (EX1001) in accordance with 35 U.S.C. §§311-319 and 37 C.F.R. §42.100 *et seq.*

The ’499 Patent discloses methods of using formulations of naltrexone, a well-known drug for treating alcoholics and heroin-dependent individuals. The ’499 Patent proposes use of a long acting formulation of naltrexone to address problems with patient compliance. EX1001, 1:25-33; EX1046, ¶63; EX1048, ¶38. Yet, it was already known that “[s]ustained-release forms of naltrexone could increase compliance and ultimately improve treatment effectiveness.” EX1004, 352.

The purported invention of the ’499 Patent calls for a known drug (naltrexone) at a known dose (about 310-480 mg) used with a known sustained release excipient (polylactide-co-glycolide, “PLGA”), to address the known problem of patient compliance. The claimed serum AUC is merely a predictable and expected result of such combination of known elements, and is also expressly disclosed in the prior art. EX1046, ¶¶64-67; EX1010; EX1011; EX1012; EX1013; EX1014; EX1016; EX1017; EX1018; EX1019; EX1020; EX1025; EX1029; EX1042; EX1056; EX1048, ¶¶39-42; EX1031.

Thus, the Examiner erred in allowing the Challenged Claims. Comparisons made to oral naltrexone treatments, and even those made during prosecution to the

depot injection formulation of Tice (EX1015), are not comparisons to the closest prior art cited here. The closest prior art actually includes identical PLGA formulations containing about 380 mg of naltrexone, administered in monthly depot injections.

Patent Owner acknowledges that pharmacokinetic results are dose dependent in this system. The claimed dose (about 380 mg), delivered from a PLGA depot injection, over the same time period, was known. The resulting AUC, a pharmacokinetic property, must therefore be the same as, or sufficiently similar to the AUC of the claimed formulation so as to render it unpatentable. The same is true for any AUC differential between depot injection and oral dosing. As the Federal Circuit has previously held in similar circumstances, “an obvious formulation cannot become nonobvious simply by administering it to a patient and claiming the resulting serum concentrations.” *Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1354 (Fed. Cir. 2012). The same should be true of the otherwise known method claimed here.

The Challenged Claims were previously challenged by a different, unrelated petitioner in IPR2018-00943. The Board instituted trial, finding it reasonably likely that the Challenged Claims would be found unpatentable over the same art cited in this Petition. EX1058. The parties subsequently settled and jointly moved to terminate the '943 IPR, and the Board granted the motion. EX1059. Given that the Board did not have the opportunity to reach final written decision in the '943 IPR,

serious unresolved questions remain concerning the validity of the Challenged Claims. Petitioner requests the Board to institute trial to resolve these questions.

II. MANDATORY NOTICES PURSUANT TO 37 C.F.R. §42.8(a)(1)

A. Real Parties-In-Interest

Pursuant to 37 C.F.R. §42.8(b)(1), Petitioner certifies that Apotex Inc. is the real party-in-interest. Additional real parties-in-interest are Artemis Parent, Inc., Artemis Intermediate Holdings, Inc., Apotex Holdco Inc., Apotex Corp., and Aposherm Delaware Holdings Corporation.

B. Identification of Related Matters Under 37 C.F.R. §42.8(b)(2)

The following is a list of any judicial or administrative matters that would affect, or be affected by, a decision in this proceeding:

Related District Court and PTAB Proceedings

Alkermes, Inc. et al. v. Teva Pharmaceutical Industries Ltd. et al., Civ. Action No. 2:20-cv-12470 (D.N.J.) (“Related Litigation”) (Terminated); and

Amneal Pharmaceuticals LLC v. Alkermes Pharma Ireland Limited, IPR2018-00943 (PTAB) (“the ’943 IPR”) (Terminated).

Related Applications

The ’499 Patent issued from U.S. Patent Application No. 11/083,167, filed on March 17, 2005 and claims priority to U.S. Provisional Application No. 60/564,542, filed on April 22, 2004.

The following applications are listed in the ’499 Patent’s continuity child data:

Petition for *Inter Partes* Review of U.S. Patent No. 7,919,499

U.S. Patent Application No. 18/243,832, filed on September 8, 2023
(abandoned);

U.S. Patent Application No. 18/099,645 (abandoned);

U.S. Patent Application No. 17/861,575, filed on July 11, 2022 (abandoned);

U.S. Patent Application No. 17/540,490, filed on December 2, 2021
(abandoned);

U.S. Patent Application No. 17/244,110, filed on April 29, 2021 (abandoned);

U.S. Patent Application No. 17/070,173, filed on October 14, 2020
(abandoned);

U.S. Patent Application No. 16/844,020, filed on April 9, 2020 (abandoned);

U.S. Patent Application No. 16/656,022, filed on October 17, 2019
(abandoned);

U.S. Patent Application No. 16/565,907, filed on September 10, 2019
(abandoned);

U.S. Patent Application No. 16/251,542, filed on January 18, 2019
(abandoned);

U.S. Patent Application No. 16/107,218, filed on August 21, 2018
(abandoned);

U.S. Patent Application No. 15/486,869, filed on April 13, 2017 (abandoned);

U.S. Patent Application No. 15/254,580, filed on September 1, 2016
(abandoned);

U.S. Patent Application No. 13/871,534, filed on April 26, 2013 (abandoned);

U.S. Patent Application No. 13/037,713, filed on March 1, 2011 (abandoned);

and

PCT International Application No. PCT/US05/09133, filed on March 18,
2005 (published).

C. Lead and Backup Counsel

Pursuant to 37 C.F.R. §§42.8(b)(3) and 42.10(a), Petitioner hereby identifies
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A Power of Attorney is being filed concurrently herewith in accordance with 37 C.F.R. §42.10(b).

D. Service Information Under 37 C.F.R. §42.8(b)(4)

Petitioners consent to e-mail service at the addresses listed above.

III. FEES

The undersigned authorizes the Office to charge Deposit Account 02-4800 for fees required by 37 C.F.R. §42.15(a).

IV. REQUIREMENTS UNDER 37 C.F.R. §42.104

A. Grounds for Standing

Pursuant to 37 C.F.R. §42.104(a), Petitioner hereby certifies that the '499 Patent is available for *inter partes* review in accordance with 37 C.F.R. §42.102(a)(2). Petitioner is not barred or estopped from requesting *inter partes* review of the challenged claims of the '499 Patent on the grounds identified herein.

B. Identification of Challenges and Precise Relief Requested

Pursuant to 37 C.F.R. §42.104(b), Petitioner challenges Claims 1-13 of the '499 Patent, and request that these claims be found unpatentable over the prior art for the reasons given below. Petitioner's Grounds for challenging the validity of the Challenged Claims are as follows:

Ground	References	Basis	Claims Challenged
1	Comer (EX1004) as evidenced by Nuwayser (EX1005)	§102(b)	1, 3-5, 12

Ground	References	Basis	Claims Challenged
2	Comer in view of Nuwayser, Rubio (EX1006), and Wright (EX1007)	§103(a)	1-13
3	Nuwayser in view of Comer, Rubio, and Wright	§103(a)	1-13

In addition to the above prior art, Petitioner relies upon evidence listed in the Exhibit List, including the Declaration and *Curriculum Vitae* of Dr. Thomas Dowling (EXs1046-1047), the Declaration and *Curriculum Vitae* of Dr. Jason Schiffman (EXs1048-1049), and the Declaration and *Curriculum Vitae* of June Ann Munford (EXs1050-1051), in their entirety.

C. Prior Art Qualification of Asserted References

The '499 Patent (EX1001) was filed on March 17, 2005 as U.S. Patent Application No. 11/083,167 (“the '167 Application”). The '167 Application claims priority to U.S. Provisional Application No. 60/564,542, filed on April 22, 2004 (EX1003).

Even if the '499 Patent is deemed entitled to its earliest priority date, all of the cited references in this Petition are prior art.

Comer (EX1004) published in 2002. EX1050, ¶¶8-14. Comer is 35 U.S.C. §102(b) prior art.

U.S. Patent No. 7,157,102 (“Nuwayser”) (EX1005), was filed on May 31, 2002, with a nonpublication request. Nuwayser is prior art under 35 U.S.C. §102(e).

Rubio (EX1006) published in 2001. EX1050, ¶¶15-21. Rubio is 35 U.S.C. §102(b) prior art.

U.S. Patent No. 6,264,987 (“Wright”) (EX1007), issued on July 24, 2001. Wright is prior art under 35 U.S.C. §102(b) and/or §102(e).

Kranzler (EX1008) published in August 1998. EX1050, ¶¶22-25. Kranzler is 35 U.S.C. §102(b) prior art.

V. BACKGROUND

A. The ’499 Patent

The ’499 Patent describes a method of treating an individual in need 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. EX1001, 1:30-46; EX1046, ¶39.

The ’499 Patent alleges that the “inventions described herein arose from unexpected discoveries made during clinical trials with a long acting formulation of naltrexone.” EX1001 Abstract, 1:31-33; EX1046, ¶40; EX1048, ¶11. ***However, the ’499 Patent provides no direct data for the AUC of any claimed formulation or the comparator—50 mg/day oral dosing.*** EX1001, 18:10-12. During prosecution, comparisons were made using data from an Alkermes’ study referenced in the ’499

Patent and from Tice. EX1002, at 300-304; EX1055. But none of this data could be determined from the '499 Patent itself.

The specification discusses a purported need for improving naltrexone therapies, based on patient compliance. EX1001, 1:13-26, 17:24-29; EX1046, ¶41. 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. EX1001, 3:14-15; EX1046, ¶42; EX1048, ¶¶12-13.

The specification describes its long-acting formulations as releasing naltrexone over a period of at least one week. EX1001, 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; EX1046, ¶42; EX1048, ¶12.

Five examples are included, three of which (Examples 3-5) were not present in the provisional application. *Compare* EX1001 *and* EX1003. 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* EX1001, 3:3-33, 5:35-8:2 *and* EX1007, 7:50-8:60. The remaining examples describe various aspects of a clinical trial and meta-analysis. Example 2 describes screening, eligibility, and adverse events. EX1001, 8:5-18:2. 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.*” EX1001, 18:10-12 (emphases added). Instead, the specification admits to using data from three nonrelated studies for a “semi-quantitative” comparison that resulted in efficacy “compares favorably with oral naltrexone.” “Favorably” in this context would be understood by a POSITA to mean comparable or equivalent to, as the ’499 Patent’s data would not establish improved efficacy to a POSITA. EX1001, 18:12-29, 19:30-33. Finally, Examples 4 and 5 are directed to “quality of life” and “durability of effect and tolerability” of long acting naltrexone formulations. EX1046, ¶¶43-45; EX1048, ¶¶14-16.

B. The ’499 Patent Examination History

The ’499 Patent was filed 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. *See also* EX1046, ¶¶38, 46-47; EX1048, ¶¶10, 17-18.

A non-final rejection was mailed on May 5, 2009 (EX1002, at 333-342), 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 (EX1002, at 291-299), with claim amendments and a declaration under 37 C.F.R. §1.132 by Elliot Ehrich (the “Ehrich Declaration” (EX1002, at 300-304; EX1055)), 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. EX1046, ¶47; EX1048, ¶18.

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. EX1002, at 276-286. Alkermes responded in an Amendment dated April 5, 2010, by amending the claims to require a biocompatible polymer. EX1002, at 177-188. A final rejection was mailed on July 20, 2010, maintaining the enablement rejection. EX1002, at 130-143. Alkermes filed a response after final on October 20, 2010, amending the claims further to require that the biocompatible polymer be PLGA. EX1002, at 121-126; EX1046, ¶48; EX1048, ¶19.

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. EX1002, at 106-114. The Examiner also included reasons for allowance, concluding that “[t]here is no prior art disclosing the applicant’s composition and effect, particularly an AUC about three times greater than that achieved by 50 mg/day oral administration”. EX1002, at 111-112. According to the Examiner, Tice (EX1009) 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. The prior art cited in this Petition discloses administering the same amount of naltrexone (about 310 mg to about 480 mg) with the same biocompatible polymer (PLGA), resulting in the same serum AUC (about three times greater than that achieved by 50 mg/day oral administration) as claimed. EX1046, ¶49; EX1048, ¶20.

C. The Terminated ’943 IPR

The ’499 Patent was previously challenged in IPR2018-00943 (“the Amneal IPR”) filed by a different petitioner, Amneal Pharmaceuticals LLC (“Amneal”). The Board instituted trial of the ’943 IPR. EX1058. Parties subsequently settled and jointly moved to terminate the IPR, and the Board granted the motion. EX1059. Given that the Amneal IPR was terminated after institution but prior to issuance of a final written decision, serious unresolved questions remain concerning the validity of the Challenged Claims of the ’499 Patent.

In the '943 IPR, the Board determined that the petitioner met its burden for purposes of institution concerning the anticipation ground based on Comer as evidenced by Nuwayser with respect to claims 1, 3-5 and 12. EX1058, 21 (“we are satisfied on this record that Comer teaches, either explicitly or inherently, each and every limitation of claim 1.”), 25 (“We have reviewed Petitioner’s contentions and supporting evidence ... and find them sufficient based on the current record for claims 3–5 and 12.”). Ground 1 of this Petition applies the same references as the above ground instituted in the '943 IPR.

In the '943 IPR, the Board also determined that the petitioner met its burden for purposes of institution concerning the obviousness ground based on the combination of Comer, Nuwayser, Rubio, and Wright with respect to claims 1-13. EX1058, 29 (“we are satisfied that Petitioner establishes sufficiently for institution that the combination of Comer and Nuwayser satisfies the limitations of claim 1. We have reviewed Petitioner’s contentions and supporting evidence regarding claims 2–13 as well, and find them sufficient based on the current record.”). Ground 2 of this Petition applies the same references as the above ground instituted in the '943 IPR.

Further, in the '943 IPR, the Board determined that the petitioner met its burden for purposes of institution concerning the obviousness ground based on the combination of Nuwayser in view of Comer, Rubio, and Wright with respect to

claims 1-13. EX1058, 29 (“...Nuwayser in view of Comer...”). Ground 3 of this Petition applies the same references as the above ground instituted in the ’943 IPR.

D. Summary of the Applied Prior Art

1. Comer (EX1004)

Comer describes a study “designed to evaluate the time course, safety, and effectiveness of a depot formulation of naltrexone (Depotrex®)” in subjects dependent on heroin. EX1004, 351 (Abstract). Comer states that the results of the study “suggest that th[e] depot formulation of naltrexone provides a safe, effective, long-lasting antagonism of the effects of heroin.” *Id.*; EX1046, ¶50; EX1048, ¶43.

As background, Comer states that, although approved as a treatment for heroin dependence, “naltrexone is generally not well accepted by patients, and medication non-compliance is a difficult obstacle to treatment.” EX1004, 351 (Abstract). Comer states, however, that “[s]ustained-release forms of naltrexone could increase compliance and ultimately improve treatment effectiveness.” *Id.*, 352. In particular, “[a] new depot formulation of naltrexone (Depotrex®) has been developed that provides a stable, long lasting elevation in plasma naltrexone levels with either no or minimal side effects.” *Id.* Comer states that “[a]lthough this formulation of depot naltrexone appears to be safe and effective in treating alcohol dependence, it has not yet been tested with heroin.” *Id.* Thus, “[t]he purpose of the current study was 1) to determine whether the new formulation of depot naltrexone will antagonize the

effects of heroin at doses comparable to those used on the streets today, and 2) to assess the duration of antagonist effect of 192 mg and 384 mg depot naltrexone.”

Id. Comer states that naltrexone microcapsules were reconstituted in a suspending medium and 2.4 ml of the suspension was injected into study participants. *Id.*, 354. Participants given a “low dose” received one placebo injection and one naltrexone injection (192 mg naltrexone base) subcutaneously into the buttocks using an 18 gauge needle. *Id.* Participants given a “high dose” received two naltrexone injections (384 naltrexone base). *Id.* Figure 1 of Comer, reproduced below, provides mean plasma levels of naltrexone as a function of depot naltrexone dosage and dates after administration of depot naltrexone. *Id.*; EX1046, ¶51; EX1048, ¶¶44-45.

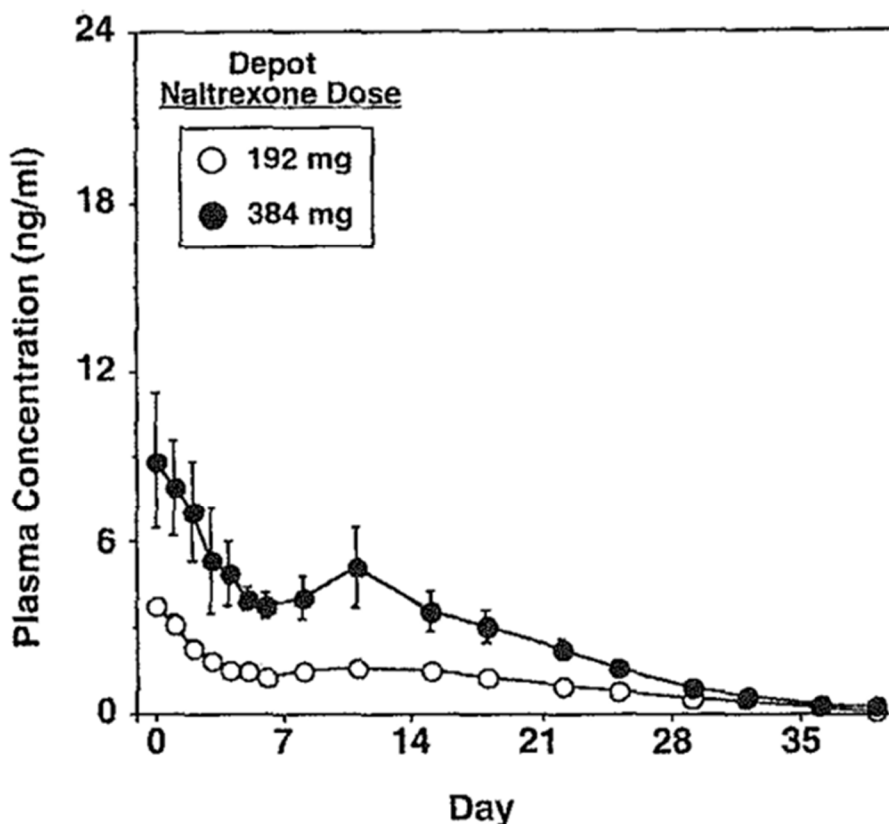


Figure 1 shows mean plasma levels of depot naltrexone over time following either a 192 mg depot dose (○) or a 384 mg depot dose (●).

Figure 1 of Comer (EX1004)

Comer states that “[a]cross the time points measured, the highest naltrexone plasma levels attained after administration of 192 mg and 384 mg of depot naltrexone were 3.8 (± 0.2) and 8.9 (± 1.4) ng/ml, respectively.” EX1004, 358. Comer states that a comparative study “reported that daily administration of 50 mg oral naltrexone resulted in naltrexone plasma concentrations of approximately 30 ng/ml, while daily administration of 12.5 mg oral naltrexone resulted in naltrexone

plasma concentrations of approximately 10 ng/ml (plasma samples were collected 30 min after administration of naltrexone).” *Id.* Thus, Comer states, “the amount of drug found in plasma after depot naltrexone administration is lower than the amount found after a standard dose of naltrexone used clinically for treating heroin dependence (50 mg/day).” Even so, “antagonism of heroin’s effects occurred, despite negligible plasma levels of naltrexone.” *Id.*; EX1046, ¶52; EX1048, ¶46.

Comer summarizes that “the data presented in the current study demonstrate that this formulation of naltrexone produced a long-lasting antagonism of the effects of intravenous heroin, with minimal side-effects.” EX1004, 359. And thus, “a formulation of naltrexone that requires only once-a-month administration has important and exciting treatment implications.” *Id.*; EX1046, ¶53; EX1048, ¶47.

The Board provided a similar summary of Comer in IPR2018-00943. EX1058, 13-16; EX1046, ¶54; EX1048, ¶48.

2. Nuwayser (EX1005)

Nuwayser teaches a multi-layered microcapsule containing one or more active ingredients and a process for preparing the microcapsule. EX1005, Abstract. In Example IV, Nuwayser teaches the preparation of naltrexone microcapsules by coating naltrexone microspheres with the polymer poly-L-(–)-lactide-co-glycolide (PLGA). *Id.*, 19:3-25. Nuwayser teaches that the microcapsules contain a final naltrexone content of 54.4%. *Id.* “This formulation delivered a therapeutic level of

naltrexone in six heroin addicts for a period of 30 days.” *Id.* Figure 7 of Nuwayser, reproduced below, provides mean plasma levels of naltrexone “after single and double [subcutaneous] injections of Depotrex™.” *Id.*; EX1046, ¶55; EX1048, ¶49.

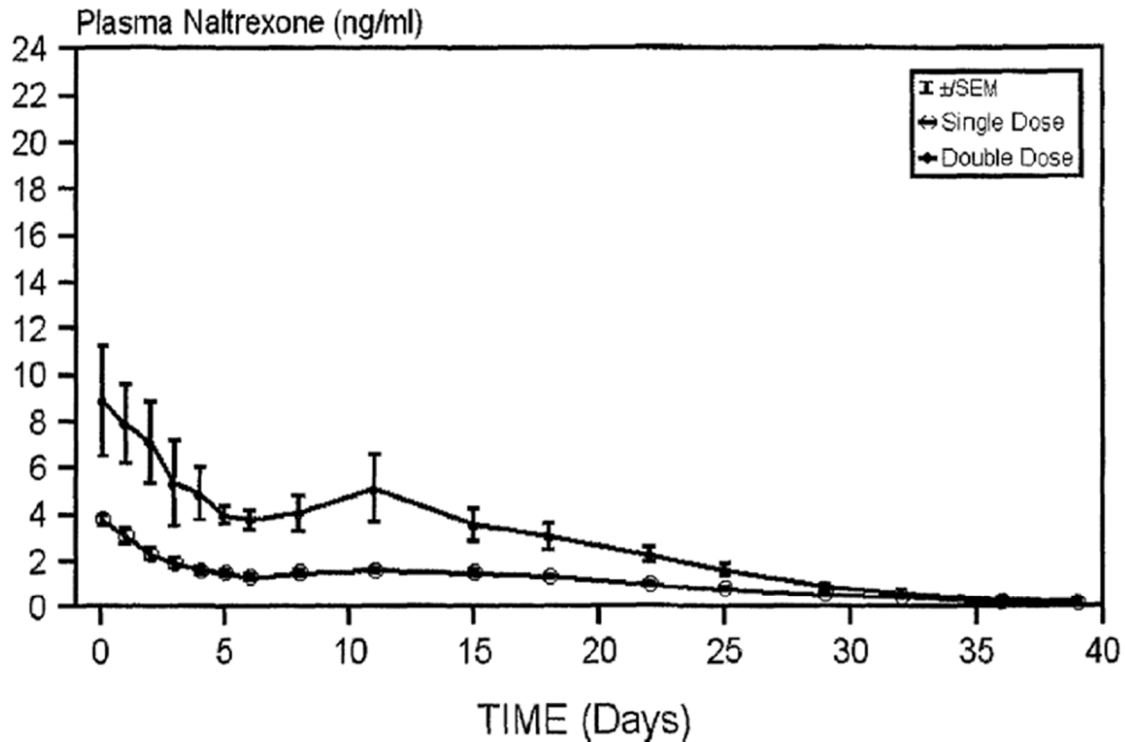


Figure 7 shows mean plasma levels of naltrexone over time following either a single dose (○) or a double dose (●) of naltrexone.

Figure 7 of Nuwayser (EX1005)

The Board provided a similar summary of Nuwayser in IPR2018-00943. EX1058, 16-17; ; EX1046, ¶56; EX1048, ¶50.

3. Rubio (EX1006)

Rubio states that both naltrexone and acamprosate “reduce relapse in alcohol dependence,” but they “have not yet been compared in a published trial.” EX1006,

419 (Abstract). Rubio describes a study designed “to compare the efficacy of these compounds in conditions similar to those in routine clinical practice.” *Id.* Recently detoxified alcohol-dependent men were administered either one year of treatment with 50 mg/day of naltrexone (*i.e.*, one tablet per day) or 1665–1998 mg/day of acamprosate (*i.e.*, six tablets per day). *Id.*; *see also id.* at 420. Rubio found that, at the end of the year, “[n]altrexone was associated with reducing relapse, achieving more days of accumulated abstinence, reducing the number of drinks consumed at any one time and reducing craving, compared to acamprosate.” *Id.* at 422; EX1046, ¶57; EX1048, ¶51.

The Board provided a similar summary of Rubio in IPR2018-00943. EX1058, 17; EX1046, ¶58; EX1048, ¶52.

4. Wright (EX1007)

Wright teaches a method for preparing microparticles having a selected polymer molecular weight. EX1007, Abstract. In Example 3, Wright teaches the preparation of microparticles containing naltrexone. *Id.* at 7:50–8:60. Wright teaches that the polymers used were “MEDISORB® 7525 DL polymer, MEDISORB® 8515 DL polymer and MEDISORB® 6535 DL polymer.” *Id.* at 7:56–58; EX1046, ¶59; EX1048, ¶53.

The Board provided a similar summary of Wright in IPR2018-00943. EX1058, 18; EX1046, ¶60.

E. Person of Ordinary Skill in the Art (“POSITA”)

A POSITA is presumed to be aware of all pertinent art, thinks along conventional wisdom in the art, and is a person of ordinary creativity. Regarding the ’499 Patent, Petitioner agrees with the POSITA definition adopted by the Board in IPR2018-00943 for purposes of this proceeding. A POSITA would have had a doctorate level degree in pharmaceuticals or related formulation sciences (such as a Pharm.D. or Ph.D.) and at least two years of experience in controlled release formulation. EX1046, ¶¶22, 31-32.

In the ’943 IPR, Patent Owner asserted that a POSITA “is experienced in the field of controlled-release formulations. This field often requires collaborative teamwork among individuals with relevant experience, including pharmaceutical scientists, clinicians, and formulation scientists. Here, a POSITA would have either a Master’s degree with at least two or three years’ experience, or have a Ph.D. or M.D. degree with at least one or two years’ experience.” EX2055, ¶28; EX1046, ¶¶33-37; EX1033; EX1052; EX1053; EX1054; EX1048, ¶¶21-22.

The Challenged Claims are unpatentable under either POSITA definition.

VI. CLAIM CONSTRUCTION

The Challenged Claims are unpatentable under all potential constructions including the constructions set forth below.

A. “the step of parenterally administering a long acting formulation comprising about 310 mg to about 480 mg of naltrexone”

In the '943 IPR, Patent Owner asserted that the phrase “the step of parenterally administering a long acting formulation comprising about 310 mg to about 480 mg of naltrexone” should be construed as “a *single injection* of a long acting formulation comprising about 310 mg to about 480 mg of naltrexone.” EX1060, 5-7 (emphasis added). The “single injection” language appears nowhere in the claims or specification, and nothing supports so limiting the claims. EX1046, ¶¶21, 94; EX1048, ¶¶23, 24.

Patent Owner pointed to the use of “*the* step” and “*a* long acting formulation” in the claims as meaning “singular.” But the opposite is true; indeed, the opposite is the rule. *See Baldwin Graphic Sys., Inc. v. Siebert, Inc.*, 512 F.3d 1338, 1342 (Fed. Cir. 2008) (“[t]his court has repeatedly emphasized that an indefinite article ‘a’ or ‘an’ in patent parlance carries the meaning of ‘one or more’.... The subsequent use of definite articles ‘the’ or ‘said’ in a claim to refer back to the same claim term does not change the general plural rule.”). That the working examples illustrate using a single shot does not mean that only one shot was claimed. This is just Patent Owner’s attempt to read limitations into the claims. EX1046, ¶95; EX1048, ¶25.

Indeed, the '499 Patent focuses on the difference between an injectable formulation given *once* every 28 days and *once-a-day* oral dosing for 28 days. In this context, clearly the '499 Patent is claiming the number of *doses used* during the

claimed period rather than how many shots, or how many pills, were needed to administer the claimed dose.

Further, claim 12 depends from claim 1 and further specifies that “naltrexone is administered **by injection**”. Under Patent Owner’s interpretation which already requires administration by injection, claim 12 would fail to further limit base claim 1 in violation of 37 C.F.R. §1.75(c) and 35 U.S.C. §112, fourth paragraph. Indeed, a POSITA would have recognized that the claimed “parenteral” administration does not require administration by injection but also encompasses administration by infusion. *See, e.g.*, EX1061, claim 1 (“composition for parenteral infusion or injection”), EX1062, 12:18-20 (“parenteral compositions for injection or infusion”), EX1063, 7:55-62 (“the parenteral route comprises subcutaneous, intramuscular and intravenous injection or infusion”). EX1046, ¶96; EX1048, ¶26.

Petitioner submits that the term “the step of parenterally administering a long acting formulation comprising about 310 mg to about 480 mg of naltrexone” should be given its plain meaning which does not exclude, *e.g.*, administration using two injections (as disclosed by Comer, see below) for the reasons explained above. EX1046, ¶97; EX1048, ¶27.

The Challenged Claims are unpatentable under both Petitioner’s and Patent Owner’s constructions as explained below.

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

The '499 Patent does not define “the serum AUC of naltrexone ... than that achieved by 50 mg/day oral administration.” EX1046, ¶98; EX1048, ¶28.

The claims require a “serum AUC” but “serum AUC” is not defined by the specification. A POSITA would appreciate that this refers to serum “area under the curve.” AUC is merely the area under a curve created by plotting plasma drug concentration versus time. As Dr. Dowling explains, a POSITA would clearly know the meaning of AUC and how it is determined. EX1046, ¶98; EX1048, ¶29.

In IPR2018-00943, the Board determined that “AUC is a well-known pharmacokinetic parameter referring to area under the curve.” EX1058, 9. The Board determined that “serum AUC is represented by a plasma concentration-time curve.” *Id.* The Board also determined that “[b]y its plain terms, claim 1 requires that the serum AUC achieved by parenterally administering the long-acting formulation of naltrexone (i.e., a long-acting formulation comprising about 310 mg to about 480 mg naltrexone and a polylactide-co-glycolide polymer as a biocompatible polymer) is about three times the serum AUC achieved by administration of a 50 mg/day oral naltrexone formulation.” EX1001, 21:3–9. Petitioner has adopted this understanding of the term “the serum AUC” for purposes of this proceeding. EX1046, ¶99; EX1048, ¶30.

The '499 Patent does not define or specify the AUC of the claimed formulation or oral dosing. However, during prosecution of the '499 Patent, Patent Owner filed a Declaration under 37 C.F.R. §1.132 (EX1002, at 300-304; EX1055) purporting to show unexpected results for the serum AUC of the claimed long-acting naltrexone formulation over that of a 50 mg/day oral formulation (i.e., an unexpected serum AUC differential). EX1055, 1–18; EX1046, ¶100; EX1048, ¶31.

The Ehrich Declaration provides two data sets (Cohort A and Cohort B) for the serum AUCs of the claimed long-acting naltrexone formulation and the 50 mg/day oral naltrexone. *See* EX1055 at 6 (Table 8). For Cohort A, the serum AUC of the 380 mg dose of the claimed long-acting naltrexone formulation is 4.307, which is 3.37 times the serum AUC value of 1.278 for the 50 mg oral naltrexone dose. *Id.* at 2. Similarly, for Cohort B, the serum AUC of the 380 mg dose of the claimed long-acting naltrexone formulation is 4.921, which is 3.35 times the 1.468 serum AUC value for the 50 mg oral naltrexone dose. *Id.* In the Examiner's Statement of Reasons for Allowance, the Examiner referenced this data as showing "an AUC about three times greater than that achieved by 50 mg/day oral administration," and explained that "no prior art disclos[es]" this effect. EX1002, at 111-112. Because these serum AUC data points were presented during prosecution and were relied on by the Examiner in allowing the application issuing as the '499 Patent, a POSITA would understand that the serum AUC achieved by 50 mg/day

oral administration encompasses these data points. Accordingly, Petitioner agrees with the Board's determination in IPR2018-00943 that "the reference to a '50 mg/day' AUC in 'than that achieved by 50 mg/day oral administration' as encompassing at least serum AUCs of 1.278 ng·day/ml and 1.468 ng·day/ml." EX1058, 11-12; EX1046, ¶101; EX1048, ¶¶32-33.

C. "about three"

The '499 Patent does not define "about three." 35 U.S.C. §112, fourth paragraph, requires that a dependent claim further narrow the scope of the claim from which it depends. Claim 5 (which depends from claim 1) specifies an AUC of about 3.3 times greater than oral dosing. Thus, "about three" necessarily encompasses at least 3.3. A POSITA would thus appreciate that "about three" also encompasses at least "about 2.7." As explained by Dr. Dowling, this term could encompass a wider range. EX1046, ¶102. Petitioner agrees with the Board's determination in IPR2018-00943 that "about three necessarily encompasses at least 3.3" and "at least about 2.7." EX1058, 13. During prosecution, Patent Owner submitted the Ehrich Declaration which provides data of a serum AUC for long-acting naltrexone formulation that is 3.3 times greater than that achieved by oral dosing. EX1055, 2. Additionally, Dr. Dowling testifies that the term "about" as used in the art encompasses "a quantity within 10%." EX1046, ¶¶102-103; EX1048, ¶34.

D. “five or 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.” EX1001, 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 term “five or more days” encompasses no prior oral naltrexone administration, *ever*. EX1046, ¶104; EX1048, ¶35.

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. EX1004, at 4-5. 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. EX1009, 5:65-6:6, 6:13-17; EX1008, 1074. Clearly the art distinguishes initial treatment doses from prior doses given for other purposes. Accordingly, “initial oral dose” as used in the ’499 Patent is an earlier *treatment* dose, not a dose provided for other purposes. EX1046, ¶¶105, 26.

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. EX1001, 6:52-54. A POSITA would appreciate that this term refers to the percent by weight of the particle. EX1046, ¶¶106-107; EX1048, ¶37.

VII. PETITIONER HAS A REASONABLE LIKELIHOOD OF PREVAILING

The following explains why Claims 1-13 of the ’499 Patent are unpatentable over the prior art asserted in Grounds 1-5. EX1046, ¶¶29-30, 108.

A. Ground 1: Claims 1, 3-5, and 12 Are Anticipated by Comer as evidenced by Nuwayser

Claims 1, 3-5, and 10-12 are anticipated by Comer.¹ As explained below, Comer describes each element claimed, including the allegedly unexpected serum AUC. Nuwayser (EX1005) evidences what a POSITA would understand from Comer's reference to "Depotrex", *e.g.*, Depotrex contains the claimed PLGA. EX1046, ¶109.

1. Claim 1 (Preamble): A method for treating an individual in need of naltrexone comprising the step of

Comer as evidenced by Nuwayser discloses the preamble of Claim 1. Comer describes testing in human opioid-dependent patients of a depot injection made from 384 mg of naltrexone (Depotrex®). EX1004, 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.*, 354. EX1004, ¶354; EX1046, ¶110.

¹ Ground 1 applies the same references as the ground based on Comer as evidenced by Nuwayser instituted in the '943 IPR. *See* §V.C.

a. [1.1]: parenterally administering a long acting formulation comprising

Comer as evidenced by Nuwayser discloses Element [1.1]. Comer seeks to provide a “sustained-release form of naltrexone” in order to “improve compliance” with patients. EX1004, 351. *See also id.*, 352. EX1046, ¶111.

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.” EX1001, 3:11-13, 3:59-64; EX1030 ¶34. Comer discloses a “sustained-release form of naltrexone” that is “long-lasting” and thus discloses a long acting formulation. EX1004, 351-352. *See also id.*, Fig 1. EX1046, ¶112.

Comer discloses “a depot formulation of naltrexone (Depotrex®)” (EX1004, 351) and while not stated in Comer, *per se*, a POSITA would understand from, for example, Nuwayser, that Depotrex® is an extended release microcapsule comprising naltrexone and PLGA. Specifically, 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.” EX1005, Fig. 7 (“Injections of Depotrex™”), 17:50-19:43. When administered subcutaneously, Depotrex delivered therapeutic levels in six heroin addicts for 30 days. *Id.*, 14:26-50, 19:4-25, Fig. 7. In addition, a POSITA 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. EX1004, at 354, Fig. 1; 1005, 19:4-25, Fig. 7. Accordingly, a POSITA would know that “Depotrex” as referenced in Comer refers to PLGA/naltrexone microcapsules used for depot injection as described in Nuwayser. Indeed, PLGA is a well-known polymer used in sustained release drug products and its use with naltrexone is not patentable. *See* EX1005. *See also, e.g.*, EX1064, 1:41-44, EX1065, [0003]-[0004], EX1066, 9:7-35. EX1046, ¶¶113-114.

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 POSITA. *In re Baxter Travenol Labs.*, 952 F.2d 388, 390-91 (Fed. Cir. 1991); *see also* MPEP §2131.01 [I], [II].

Comer’s depot formulation was injected into the buttocks of the patients using an 18 gauge needle—*i.e.*, satisfying the claimed parenteral administration. EX1004, 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.*, 351. “These results suggest that this depot formulation of naltrexone provides a safe, effective, long-lasting antagonism of the effects of heroin.” *Id.* EX1046, ¶115.

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). EX1046, ¶116.

Comer's Depotrex does not lack the claimed PLGA. In the '943 IPR, Patent Owner asserted that Comer does not anticipate because “different versions of Depotrex existed” and pointed to Kranzler (EX1008) for support. EX1058, 23-24. Such argument is untenable for three reasons. First, Patent Owner conceded that Kranzler does not even mention “Depotrex”, much less establish that a different “version” of Depotrex existed that somehow differed from what was used in Comer. EX1060, 46 (“Kranzler makes no mention of DepotrexTM”). Second, Patent Owner overlooks the explanation in Comer and Kranzler that the preparations were merely being reconstituted to different concentrations (192 mg in 2.4 mL and 206 mg in 2.4 ml, respectively). EX1004, 354 (“After reconstituting in suspending medium...”); EX1008, 1076 (“the microcapsule preparation was reconstituted in a suspending medium”). Third, Patent Owner does not even assert much less demonstrate that a Depotrex formulation existed that did not contain PLGA—the only claimed component not expressly mentioned in Comer. Indeed, Patent Owner proffered its “different Depotrex version” theory in its Preliminary Response but dropped it in its Patent Owner Response when faced with the possibility of cross-examination. EX1046, ¶¶61-62.

b. [1.2]: about 310 mg to about 480 mg of naltrexone

Comer as evidenced by Nuwayser discloses Element [1.2]. Comer discloses that the two 192 mg naltrexone injections constitute a single “administration” of 384 mg naltrexone, *i.e.*, a single “high dose” of naltrexone. EX1004, 354, Fig. 1. As discussed above with respect to the preamble, Comer describes testing in human opioid-dependent patients of a depot parenteral administration made from 384 mg of naltrexone (Depotrex®). EX1004, at 351-354. Comer discloses that “[t]he active formulation contained drug equivalent to 192 mg naltrexone base...and for the high dose, participants received two naltrexone injections”, *i.e.*, “administration of ... 384 mg depot naltrexone.” EX1004, 354. *See also id.*, Fig. 1 (“Depot Naltrexone Dose ... 384 mg”). EX1046, ¶117.

As explained above in Section VI.A., the phrase “the step of parenterally administering a long acting formulation comprising about 310 mg to about 480 mg of naltrexone” does not exclude the two injections of Comer. Comer’s administering of the “high dose” constituting two 192 mg naltrexone injections (*i.e.*, 384 mg) satisfies the claimed step of parenterally administering a long acting formulation comprising about 310 mg to about 480 mg of naltrexone. Indeed, Comer itself refers an “administration of ... 384 mg depot naltrexone” (EX1004, 354) recognizing that the two 192 mg naltrexone injections constitute a single “high dose” administration of naltrexone. EX1046, ¶118.

c. [1.3]: and a biocompatible polymer to the individual

Comer as evidenced by Nuwayser discloses Element [1.3]. As discussed above with respect to Element [1.1], Comer as evidenced by Nuwayser discloses a formulation comprising PLGA (65% lactide: 35% glycolide, or 65% LA: 35% GA), identified as “Depotrex.” EX1004; EX1005, 14:26-50, 19:4-25, Fig. 7. As explained above in Section VII.A.1.a., there is no evidence demonstrating that Comer’s Depotrex lacks the claimed PLGA. In the ’943 IPR, Patent Owner did not even assert much less demonstrate that a Depotrex formulation existed that did not contain PLGA—the only claimed component not expressly mentioned in Comer. Indeed, in the ’943 IPR, the Board correctly determined that “an ordinarily skilled artisan would understand Comer’s ‘Depotrex®’ formulation refers to ‘naltrexone and a biocompatible polymer . . . wherein the biocompatible polymer is a polylactide-co-glycolide polymer,’ as recited in claim 1”. EX1058, 21. Thus, Comer as interpreted by Nuwayser discloses Element [1.3]. EX1046, ¶119.

d. [1.4]: wherein the serum AUC of naltrexone is about three times greater than that achieved by 50 mg/day oral administration

Comer as evidenced by Nuwayser discloses Element [1.4]. As discussed by Dr. Dowling, the plot of Figure 1 of Comer discloses a serum AUC that is about three times greater than that achieved by 50 mg/day oral administration to the same

extent as the '499 Patent. EX1046, ¶¶68-79, 120-121; EX1034; EX1035; EX1039; EX1040; EX1041.

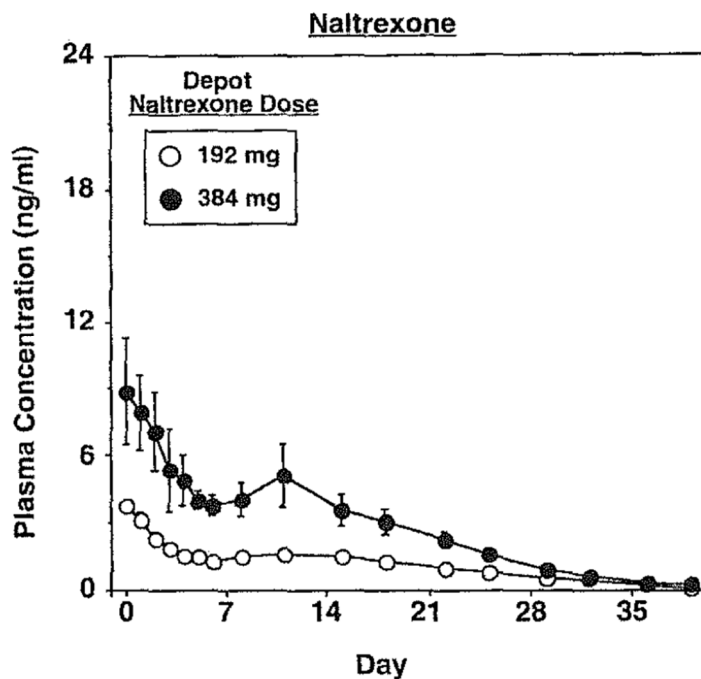


Figure 1 of Comer (EX1004)

This differential results from comparing the AUC of Comer to the oral data presented in the Ehrich Declaration, the same oral data used by Patent Owner when making its comparison.

Dr. Dowling determined the AUC of Comer using the linear trapezoid rule. See Appendix A for the linear trapezoid rule formula; EX1046, ¶80. In particular, he determined each of the plasma concentrations from Figure 1 over the course of 28 days, *e.g.*, 8.9 ng/mL at the 2 hour mark. See Appendix A; EX1046, ¶81. Once these individual plasma concentrations were determined, Dr. Dowling used the

linear trapezoid rule to calculate the AUC of each time interval, *e.g.*, 0 to 2 hours, 2 hours to 1 day, etc. *See* Appendix A; EX1046, ¶81. Finally, he summed the individual AUC values to obtain an AUC_{0-28d} of 104.20 ng·day/mL for the Comer 384 mg administered dose (EX1004 Abstract, 354). *See* Appendix A; EX1046, ¶82. He then divided the Comer AUC_{0-28d} value of 104.20 ng·day/mL by the 50 mg/day oral dose provided in the Ehrich Declaration, *i.e.*, 35.78 ng·day/mL to yield a differential of 2.9. *See* Appendix A; EX1046, ¶88. So Comer's AUC differential over 50 mg/day oral dosing is about 3, indeed about 2.9. *See also* Appendix A. EX1046, ¶88.

Dr. Dowling also evaluated the AUC calculation provided by Dr. Kinam Park in the '943 IPR and found Dr. Park's methodology to be accurate and Dr. Park's Comer differential to be consistent with that determined by Dr. Dowling. EX1046, ¶¶83-88.

During an appeal filed in the '499 Patent's grandchild, Application No. 13/871,534, filed April 26, 2013 (now abandoned), Patent Owner admitted that "[t]he Examiner appears to ignore the fact that the result (superior efficacy and pharmacokinetic profile) is dose dependent...." EX1021, at 7. The dose of Comer is 384 mg, which is 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 Patent Owner relied for their observation of alleged unexpected results. EX1001, 1:30-

40, 8:32-4, 17:49-62. Since the doses are the same and Patent Owner has admitted that AUC is dose dependent, Comer must also have the disclosed AUC differential if compared to the same oral dosing data. EX1046, ¶122.

e. [1.5]: and wherein the biocompatible polymer is a polylactide-co-glycolide polymer.

Comer as evidenced by Nuwayser discloses Element [1.5] . As discussed above with respect to Elements [1.1] and [1.3], Comer as interpreted by Nuwayser discloses a formulation comprising PLGA (65% lactide: 35% glycolide, or 65% LA: 35% GA), identified as “Depotrex.” EX1004; EX1005, 14:26-50, 19:4-25, Fig. 7. As explained above in Section VII.A.1.a., there is no evidence demonstrating that Comer’s Depotrex lacks the claimed PLGA. In the ’943 IPR, Patent Owner did not even assert much less demonstrate that a Depotrex formulation existed that did not contain PLGA—the only claimed component not expressly mentioned in Comer. EX1046, ¶123.

Thus, Comer as evidenced by Nuwayser anticipates Claim 1. EX1046, ¶124.

2. Claim 3: The method of claim 1 wherein the long acting formulation releases naltrexone for a period of at least two weeks.

Comer discloses the subject matter of Claim 3. Comer’s release for a month anticipates Claim 3, requiring at least two weeks of naltrexone release. *See, e.g.*, EX1004, Figure 1, 359 (“formulation of naltrexone that requires only once-a-month administration has important and exciting treatment implications”). EX1046, ¶125.

3. Claim 4: The method of claim 1 wherein the long acting formulation releases naltrexone for a period of about four weeks.

Comer discloses the subject matter of Claim 4. Comer's release for a month anticipates Claim 4, requiring release for four weeks. *See, e.g.*, EX1004, Figure 1, 359 ("formulation of naltrexone that requires only once-a-month administration has important and exciting treatment implications"). EX1046, ¶126.

4. Claim 5: The method of claim 1 wherein the long acting formulation is administered in a dose of about 380 mg of naltrexone wherein the serum AUC is about 3.3 times greater than that achieved by 50 mg/day oral administration.

Comer discloses the subject matter of Claim 5. The AUC differential resulting from the comparison of Comer to the Ehrich Declaration, as previously discussed, shows a differential of about three, indeed about 2.9. EX1046, ¶127.

However, if instead of using the oral data provided by the Ehrich Declaration, the oral AUC_{0-28d} data found in Tice (EX1009, 14:34-58) is used, the mean AUC_{0-28d} of Comer is 3.2 times greater than the oral AUC_{0-28d}. ($\frac{103.7}{(27.8+24) \times 28} = 3.2$). And if the higher end of the standard deviation of Comer is used, then the AUC differential is 3.9 times greater than the oral AUC_{0-28d} used in the Tice patent ($\frac{125.4}{(27.8+24) \times 28} = 3.9$). EX1046, ¶¶89-90, 127.

Thus, Comer discloses a serum AUC that is about 3.3 times greater than that achieved by 50 mg/day oral administration. EX1046, ¶128.

5. Claim 12: The method of claim 1 wherein naltrexone is administered by injection.

Comer discloses the subject matter of Claim 12. As noted in connection with Claim 1, Comer discloses administering two naltrexone injections into the buttocks, so claim 12 is anticipated. Comer discloses that the two naltrexone injections constitute a single “administration”, *i.e.*, a “high dose” of naltrexone as explained above. EX1004, at 354; EX1046, ¶129.

B. Ground 2: Claims 1-13 Would Have Been Obvious Over Comer in view of Nuwayser, Rubio, and Wright

Claims 1-13 would have been obvious over Comer in view of Nuwayser, Rubio and Wright.² EX1046, ¶¶130-134.

1. Claim 1

Comer in view of Nuwayser disclose and suggest each feature of claim 1. One, to the extent Patent Owner asserts that Nuwayser does not constitute evidence of the Depotrex formulation disclosed by Comer, it would have been obvious to use the Nuwayser naltrexone formulation containing PLGA in the method taught by Comer. Two, it would have been obvious to modify Comer to employ a single high dose

² Ground 2 applies the same references as the ground based on Comer in view of Nuwayser, Rubio, and Wright instituted in the '943 IPR. *See* §V.C.

injection of naltrexone—thus satisfying Patent Owner’s erroneous “single injection” construction from the ’943 IPR. EX1046, ¶130.

It would have been obvious to use the Nuwayser naltrexone formulation containing PLGA in the method taught by Comer

Comer and Nuwayser are described in above 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). Comer does not expressly discuss that Depotrex formulation contains PLGA. But a POSITA interested in Depotrex would find Nuwayser, which describes Depotrex fully. EX1046, ¶135.

If one did not accept that Nuwayser defined Depotrex used in Comer to a POSITA as explained in Ground 1, a POSITA would nonetheless have had reason and been 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 POSITA would seek out acceptable formulations. Comer teaches a method of treating heroin addicts by using 384 mg naltrexone in parentally injectable naltrexone-containing microcapsules. EX1004, at 351, 354, 358-359, Fig. 1. But except for the dose, Nuwayser teaches the same thing. EX1005, 19:4-25. And both

provide data on the release profile of their formulations, which a POSITA would recognize to be the same, or nearly so. EX1004, Fig. 1; EX1005, Fig. 7. EX1046, ¶136.

A POSITA 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. 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. Indeed, as Dr. Dowling noted, when the AUCs of Comer and Nuwayser are compared to the oral data in the Ehrich Declaration, the AUC differential is about three, indeed about 2.9. EX1046, ¶137.

Given the sameness of the AUC plots of Comer and Nuwayser, and that both stated that they provided therapeutic doses for about a month, a POSITA would also have a reasonable expectation that their combined teachings would be successful. EX1004, 351, 359 (“These results suggest that this depot formulation of naltrexone provides a safe, effective long-lasting antagonism of the effects of heroin.”); EX1005, 19:23-25 (“This formulation delivered a therapeutic level of naltrexone in six heroin addicts for a period of 30 days (*see* FIG. 7).”). EX1046, ¶138.

But even if the claimed AUC differential did not result from this combination, the claims would still be obvious because this limitation should be given little weight. First, as Dr. Dowling explains, a POSITA 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. 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). Indeed, as Dr. Dowling explains, it is even possible that an enhanced AUC above levels necessary to minimally maintain therapeutic blood levels could raise toxicity issues. EX1046, ¶139.

Nothing in the specification would suggest to a POSITA 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. A depot injection might provide better compliance, but that was known. EX1004, 351-352. Indeed, when distinguishing oral dosing and other depot injections during prosecution, Alkermes noted that Tice (EX1009) resulted in an AUC that was roughly the same as oral dosing—not three times that level as claimed. EX1055 at 4. Alkermes did not argue, however, that either was less effective. EX1046, ¶140.

Moreover, a POSITA 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. Instead, a POSITA 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. 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 POSITA would understand that the AUC and differential should all be the same or not patentably different. EX1046, ¶141.

A POSITA 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. Accordingly, a POSITA 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. EX1046, ¶142.

It would have been obvious to modify Comer to employ a single high dose injection of naltrexone

In the '943 IPR, Patent Owner asserted that claim 1 should be construed to require a "single injection" of naltrexone, and that such construction excludes the

two naltrexone injections of Comer's "high dose" administration. EX1060, 5-7, 13-14. However, as explained in Section VI.A., the "single injection" language of Patent Owner's construction appears nowhere in the claims or specification, and nothing supports so limiting the claims. As noted above, Comer discloses that the two 192 mg naltrexone injections constitute a single "administration" of 384 mg naltrexone, *i.e.*, a single "high dose" of naltrexone, satisfying claim 1. Nonetheless, it also would have been obvious to modify Comer to administer the "high dose" (384 mg) naltrexone with a single injection. This is true for a number of reasons discussed below. EX1046, ¶131; EX1048, ¶54.

The efficacy of naltrexone in treating drug dependencies was known to be limited by poor patient compliance or adherence to the prescribed daily dosing. EX1004, 351. A POSITA would have recognized potential drawbacks of subjecting patients to multiple (192 mg) injections of naltrexone for the purpose of administering a single "high dose" (384 mg) of naltrexone, as is the case in Comer. EX1046, ¶132; EX1048, ¶55.

Patients having opioid use disorder and alcohol use disorder have been known to have difficulties complying with naltrexone treatment for a number of reasons. By 2003, the efficacy of naltrexone in treating alcohol and opioid use disorders was known to be limited by poor patient compliance or adherence to the prescribed daily dosing. Patient adherence is particularly important in treating alcohol and opiate

dependence because the compulsion to self-administer drugs directly conflicts with the need to remain abstinent. This daily conflict further exacerbates problems of poor adherence, contributing to the spiral towards relapse common to both maladies. EX1048, ¶56.

Factors affecting a patient's drug compliance or adherence to prescribed treatment may be categorized to patient-centered factors, therapy-related factors, social and economic factors, healthcare system factors, and disease factors. Patient-centered factors include psychological factors (e.g., beliefs, motivation, and attitude), physical impairments, and effects of substance use. Therapy-related factors include route of administration, dosing frequency, treatment complexity, frequency of office visits, and duration of the treatment period. EX1048, ¶57.

It has been well-established that reducing the number of injections administered to patients would offer benefits for the patient's health outcomes and adherence to the prescribed treatment. For example, increasing the number of injection administered to patients has been long recognized as a factor contributing to noncompliance. Extended-release formulations have been widely used to allow reduction of the number of injections administered to patients, which may enhance convenience and thereby improve adherence. EX1048, ¶58.

Patients receiving a drug treatment via intramuscularly injection may have a wound at the injection site and develop inflammation. In addition, intramuscular

injections allow for the potential introduction of bacteria and other pathogens into the patient. These intramuscular injections can have commonly known complications such as muscle damage, nerve damage, potential for injecting into a blood vessel (which can result in a hematoma), and the potential for the abscess formation. More serious complications from intramuscular injections can result in tissue necrosis, granulomas, muscle fibrosis as well as other complications. Patients receiving intramuscular injections often experience significant pain with these injections thereby decreasing their motivation to receive these injections. EX1046, ¶¶132, 158; EX1048, ¶59.

Additional effects of intramuscular injections can result in the liquid formulation of the drug being administered leaking out of the injection site thereby reducing the dosage amount that patient actually receives. EX1046, ¶132; EX1048, ¶60.

Administering an amount of medication to a patient as two separate intramuscular injections each containing half the dose rather than as a single intramuscular injection containing the entire dose doubles the risk of these complications and the discomfort that the patient must endure and further decreases their motivation to continue treatment. EX1048, ¶61.

Further, as a practical matter, administering two doses of a medication doubles the operational burden on a medical practice, it doubles the administrative costs with

administering such injections, and also doubles the risk of adverse events. All of which must be addressed by the medical practice. EX1048, ¶62.

Therefore, it would be self-evident to a POSITA that administration of a dose of a drug as a single intramuscular injection would be desirable in comparison with administration of that same dose as two separate intramuscular injections as the latter increases the risk of adverse events, increases patient discomfort, and increases administrative burden on the medical practice, all without providing any increase in benefit. EX1048, ¶63.

In addition, Comer, itself, provides motivation for a POSITA to reduce the number of depot injections of a long-acting naltrexone formulation. For example, Comer describes “[e]leven of 12 participants report[ing] pain during administration of the depot injections.” EX1004, 357. Indeed, the “discomfort associated with the actual injections of depot naltrexone and mild soreness at the injection site [continued] for 2-3 days following the injections.” *Id.*, 359. Thus, for example, a POSITA would have been motivated to reduce pain associated with multiple injections by reducing two injections to just one. EX1046, ¶¶133, 159.

A POSITA would have recognized the drawbacks of subjecting patients to multiple (192 mg) injections of naltrexone for the purpose of administering a single “high dose” (384 mg) of naltrexone, as is the case in Comer, and would have had reason and been motivated to modify Comer to employ a single 384 mg naltrexone

injection as opposed to two separate 192 mg injections with a reasonable expectation of success. Such a modification would have merely constituted combining prior art elements (two injections) according to known methods to yield predictable results. While Comer employed a single injection composition of naltrexone for both the low and high doses and increased the dose by simply employing two injections, a POSITA would have recognized that employing a single injection containing the total 384 mg naltrexone would have been a desirable alternative to avoid the above potential drawbacks of multiple injections, yielding only predictable results. EX1046, ¶¶134, 160. EX1048, ¶64.

A POSITA would have had a reasonable expectation of success to employ a single 384 mg naltrexone injection as opposed to two separate 192 mg injections for the reasons discussed above. Further, Comer states that “after reconstituting in suspending medium, 2.4 ml of the suspension was injected. The active formulation contained drug equivalent to 192 mg naltrexone base.” EX1004, 354. This equates to a dosage concentration of 80 mg/mL, and the volume of a single injection at this concentration would be 4.8 mL, which a POSITA would consider to be an acceptable volume for intramuscular injection. A POSITA would have also recognized that naltrexone would be reconstituted at higher concentrations if a smaller volume was desired. *See, e.g.*, EX1008, 1075 (206 mg naltrexone in 2.4 ml). Optimization of the concentration and volume of the injectable composition would have been well within

the skill of a POSITA. Indeed, the '499 Patent does not specify any volume requirements of the injectable and itself employed larger injection volumes (*e.g.*, 4 mL) without concern. EX1001, 5:10-12. EX1048, ¶¶65-66.

2. Claim 2

Comer in view of Nuwayser disclose and suggest the subject matter of claim 2. Claim 2 recites “The method of claim 1 comprising administering the long acting formulation comprising naltrexone every four weeks for a period of about 24 weeks or more wherein the individual has not used oral naltrexone within five or more days before said administration”. EX1046, ¶143.

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.” EX1004, at 351. Moreover, Rubio teaches that treatment protocols of 12 months in alcoholics were known. EX1006, at 419-420. Long term treatment of six months or more was known. *See, e.g.*, EX1037 Abstract; EX1038 Abstract. As to the latter limitation, Comer contemplated treating with the depot injection without a prior oral dose of naltrexone. EX1004, 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. EX1046, ¶144; EX1037; EX1038.

3. Claim 3

Comer in view of Nuwayser disclose and suggest the subject matter of claim 3 as explained above in Ground 1. 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. EX1046, ¶145.

4. Claim 4

Comer in view of Nuwayser disclose and suggest the subject matter of claim 4 as explained above in Ground 1. EX1046, ¶146.

5. Claim 5

Comer in view of Nuwayser disclose and suggest the subject matter of claim 5 as explained above in Ground 1. Further, 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 falls within the margin of error in measurement. EX1046, ¶147.

6. Claim 6

Comer in view of Nuwayser disclose and suggest the subject matter of claim 6. Claim 6 recites “The method of claim 1 wherein the long acting formulation is

administered over a period of about 24 week period or longer.” Comer discloses and suggests the subject matter of Claim 6. This is obvious for the reasons described in connection with claim 2, which includes the same limitation. EX1046, ¶148.

7. Claims 7-9

Comer in view of Nuwayser disclose and suggest the subject matter of claims 7-9. Claim 7 recites “The method of claim 1 further comprising a second administration of a long acting formulation comprising naltrexone at least about 7 days after the first administration.” Claim 8 recites “The method of claim 7 wherein the second long acting formulation is substantially similar to the first long acting formulation.” Claim 9 recites “The method of claim 7 wherein the second long acting formulation is the same as the first long acting formulation.” EX1046, ¶149.

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. As Dr. Dowling explains, this protocol would be obvious to a POSITA. Since Comer and Nuwayser both teach four-week dosing, a POSITA would not consider a second dose earlier than seven days. 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 POSITA 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. EX1046, ¶150.

8. Claim 10

Comer in view of Nuwayser disclose and suggest the subject matter of claim 10. Claim 10 recites “The method of claim 1 wherein the individual is an individual afflicted by alcohol dependency.” The patients in the Comer study were opioid dependent. But Comer acknowledged that naltrexone had already been established to be safe and effective in alcoholics. EX1004, at 352. So to a POSITA, Comer’s result also places the art in possession of treating an alcoholic with a 384 mg depot injection as claimed. Rubio teaches treating alcoholics with naltrexone as well. EX1006, at 419-420. EX1046, ¶151.

9. Claim 11

Comer in view of Nuwayser disclose and suggest the subject matter of claim 11. Claim 11 recites “The method of claim 1 wherein the individual does not receive an initial oral dose of naltrexone.” In Comer, patients did get oral naltrexone, but they did not get the depot injection until two days later. EX1004, at 353. Oral naltrexone was administered “to ensure that participants were willing and able to tolerate its effects”—not as part of the same “method for treating an individual in need of naltrexone”, as required in claim 11. EX1004, 353. That oral dosing in Comer was not an “initial” treatment dose, as it was given for other purposes. *See*

also EX1004, at 359 (“In a treatment setting where oral naltrexone may not be given prior to depot naltrexone....”). Moreover, there is no oral dosing suggested in Nuwayser. Claim 11 is therefore obvious. EX1046, ¶152.

10. Claim 12

Comer in view of Nuwayser disclose and suggest the subject matter of claim 12. Claim 12 requires that the parenteral administration be an injection. Comer teaches injection into the buttocks. EX1004, at 354. Nuwayser teaches subcutaneous (“SC”) injection. EX1005, Fig. 7. Claim 12 is therefore obvious. EX1046, ¶153.

11. Claim 13

Comer in view of Nuwayser disclose and suggest the subject matter of claim 12. Claim 13 recites “The method of claim 1 wherein the naltrexone is present in the long acting formulation at a concentration of about 35% by weight.” While Nuwayser exemplifies a formulation that includes naltrexone in the amount of 54.4% by weight (EX1005, 19:22-23), Wright demonstrates that it was well-known to employ naltrexone drug loading in the range of 30-75% by weight of the formulation. EX1007, 7:63-8:1. *See also id.*, 12:8-32 (disclosing the use of PLGA microparticles). Thus, the claimed naltrexone concentration is encompassed by the range contemplated by the prior art and is not patentable, *e.g.*, given that a POSITA would have had reason to optimize the concentration of the naltrexone formulation

in view of the fact that the prior art teaches the general conditions of the Challenged Claims, explained above. EX1046, ¶154.

C. Ground 3: Claims 1-13 Would Have Been Obvious Over Nuwayser in View of Comer, Rubio, and Wright

Claims 1-13 would have been obvious over Nuwayser in view of Comer, Rubio, and Wright.³ EX1046, ¶155.

As discussed below, Nuwayser identifies a naltrexone/PLGA depot injection formulation, a treatment protocol, and the pharmacokinetic plot that results from its administration. Nuwayser is not explicit as to the dose providing that plot. But in seeking to determine that dose, a POSITA would find Comer, which used the same protocol, resulting in an identical plasma level plot, and used about 380 mg of naltrexone to do so. EX1046, ¶¶91-93, 155; EX1057.

1. Claim 1 (Preamble)

Nuwayser discloses and suggests the preamble of Claim 1. In Example IV, Nuwayser describes a formulation of PLGA (65% LA: 35% GA) and 54.4% naltrexone, described as Depotrex, which, when administered subcutaneously,

³ Ground 3 applies the same references as the ground based on Nuwayser in view of Comer, Rubio, and Wright instituted in the '943 IPR. *See* §V.C.

delivered therapeutic levels in six heroin addicts for 30 days. EX1005, 14:26-50, 19:4-25; EX1046, ¶156.

As explained in Section VI.A., the “single injection” language of Patent Owner’s construction from the ’943 IPR appears nowhere in the claims or specification, and nothing supports so limiting the claims. Further, for at least the reasons discussed above in Section VII.B.1. (Ground 1), it would have been obvious to modify Nuwayser-Comer to employ a single high dose injection of naltrexone—thus satisfying Patent Owner’s erroneous “single injection” construction. EX1046, ¶157.

a. Element [1.1]

Nuwayser discloses and suggests Element [1.1]. As discussed above, Nuwayser discloses that Depotrex—a long acting formulation—was administered subcutaneously, *i.e.*, thus satisfying “parenterally”. Thus, Nuwayser discloses Element [1.1]. EX1046, ¶161.

b. Element [1.2]

Nuwayser discloses and suggests Element [1.2]. For example, in Figure 7, Nuwayser shows the naltrexone plasma level of the six human heroin addicts described in Example IV after single and double SC injections of Depotrex.

Figure 7. Naltrexone Plasma Level in Six Human Subjects After Single and Double SC Injections of Depotrex™

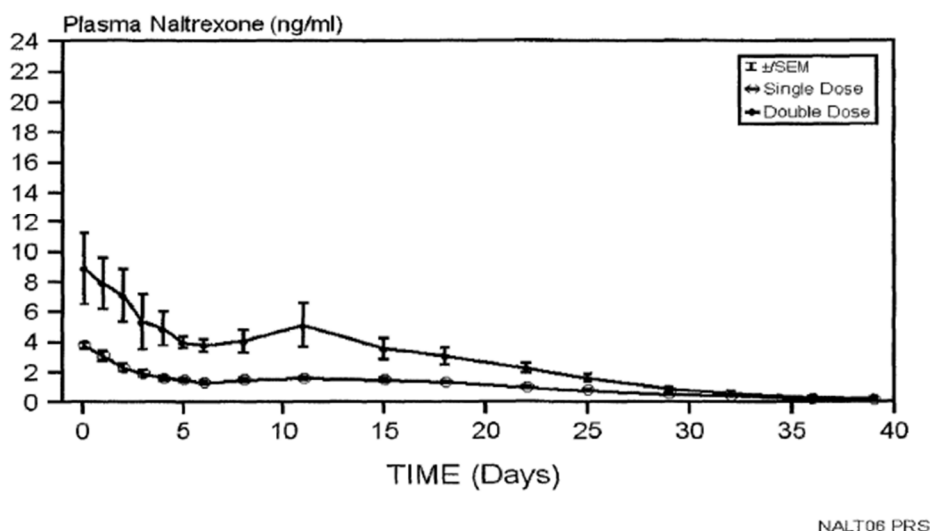


Figure 7 of Nuwayser (EX1005)

The data in that figure demonstrates that the total AUC discloses a dose of about 380 mg by integration of the plot of Figure 7. This falls within the claimed range of 310-480 mg. EX1005, 19:4-25, Fig. 7; EX1046, ¶¶162-163.

It would have been obvious to administer 384 mg naltrexone in view of Comer. Nuwayser describes formulations of extended release microcapsules of naltrexone (65:35 PLGA and 54.4% naltrexone by weight) and explains that the microcapsules can be subcutaneously implanted in heroin dependent patients to provide therapeutic levels of naltrexone for a period of 30 days. EX1005, 14:26-49, 19:4-25, Fig. 7. Nuwayser provides a plot of the pharmacokinetics, including the AUC resulting from the use of these microcapsules. The only thing that Nuwayser arguably does not explicitly disclose is the dose—how much of the formulation

made in accordance with its Examples II and IV is needed to provide the AUC plot in Fig. 7. EX1046, ¶164.

However, like Nuwayser, Comer describes giving long-acting naltrexone parenterally to six heroin dependent patients where a therapeutic level was delivered for about a month. Indeed, both references administered “Depotrex” produced by the same manufacturer, Biotek Inc. In addition, Dr. Nuwayser is both an author of Comer and an employee of Biotek. Finally, in both, the pharmacokinetic plots were reported and are superimposable. *Compare* EX1004, Fig. 1 *with* EX1005, Fig. 7. All of this would have motivated a POSITA looking for an appropriate dose to use that disclosed in Comer, namely 384 mg (about 380 mg). EX1046, ¶165.

And a POSITA would have had a reasonable expectation of success given the success reported by both Nuwayser and Comer and the near identity of their disclosed protocols and pharmacokinetic plots. Indeed, one would have a reasonable expectation that the AUC results of the combination would be those reported in the figures of both Nuwayser and Comer. Moreover, as described previously, since the doses of Comer and Nuwayser are about 380 mg, and since AUC is dose-dependent, the AUC should be the same, and the same as that resulting from the formulation claimed in the ’499 Patent (380 mg). EX1046, ¶166.

The AUC differential resulting from the combination should be the same as that claimed as well, assuming that the same oral dose data is used. Using the

inventor's data and/or that of Tice, the AUC differential would be about three, indeed about 2.9. EX1046, ¶167.

To the extent that the dose did not provide the AUC of Nuwayser's Figure 7, as the claimed AUC differential, a POSITA could adjust the dose to arrive at that disclosed AUC endpoint of Figure 7. A POSITA could do so assuming that a POSITA considered the AUC differential to be significant, which, as discussed in connection with claim 1 of Ground 3, a POSITA would not. EX1046, ¶168.

c. Element [1.3]

Nuwayser discloses and suggests Element [1.3]. As discussed above, Nuwayser discloses that Depotrex—a formulation comprising biocompatible polymer, PLGA—was administered to six heroin addicts. Thus, Nuwayser discloses Element [1.3]. EX1046, ¶169.

d. Element [1.4]

Nuwayser discloses and suggests Element [1.4]. For example, in Figure 7, Nuwayser shows the naltrexone plasma level of the six human heroin addicts described in Example IV after single and double SC injections of Depotrex. The data in that figure demonstrates that plasma levels of 1 ng/ml could be obtained for at least 28 days. EX1005, 19:4-25, Fig. 7; EX1046, ¶170.

Further, since the plot of Nuwayser is superimposable with that of Comer, the AUC and the AUC differential for Nuwayser must be the same as for Comer,

assuming again that the same comparison is made. Moreover, since “superior efficacy and pharmacokinetic profile” are dose dependent EX1021, at 7, the dose disclosed by Nuwayser must be substantially the same as that given in the clinical study (380 mg) described in the ’499 patent and the Ehrich Declaration and disclosed in Comer. EX1046, ¶171. Since the doses must be the same, the AUC and differential (based on the oral data used by Alkermes) must be the same.

e. Element [1.5]

Nuwayser discloses and suggests Element [1.4]. As discussed above, Nuwayser discloses that Depotrex—a formulation comprising biocompatible polymer, PLGA—was administered to six heroin addicts. Thus, Nuwayser discloses Element [1.5]. EX1046, ¶¶172-173.

Accordingly, Nuwayser renders obvious Claim 1 of the ’499 Patent.

2. Claim 2

Nuwayser in view of Comer disclose and suggest the subject matter of claim 2. *See* §VII.B.2 (Ground 1, claim 2). Claim 2 is obvious because Nuwayser does not require any prior oral dose and Comer contemplates this as well. Six or more treatments every 4 weeks was also well known. EX1004, at 352; EX1006, at 419, 420; EX1046, ¶174.

3. Claim 3

Nuwayser in view of Comer disclose and suggest the subject matter of claim 3. *See* §VII.B.3 (Ground 1, claim 3). Nuwayser’s 28-day release satisfies claim 3,

requiring at least two weeks of naltrexone release. Indeed, both Nuwayser and Comer teach one-month dosing and render obvious claim 3. EX1046, ¶175.

4. Claim 4

Nuwayser in view of Comer disclose and suggest the subject matter of claim 4. *See* §VII.B.4 (Ground 1, claim 4). Nuwayser's 28-day release satisfies claim 4, requiring release for four weeks. Indeed, both Nuwayser and Comer teach one-month dosing and render obvious claim 4. EX1046, ¶176.

5. Claim 5

Nuwayser in view of Comer disclose and suggest the subject matter of claim 5. *See* §VII.B.5 (Ground 1, claim 5). Claim 5 is obvious because both Nuwayser and Comer teach administering about 380 mg of naltrexone and render a difference in AUC of 3.3 obvious. As noted just above, Nuwayser teaches administering about 380 mg and the resulting AUC. This is the same dose as Comer, and the AUC differential (assuming the same oral data is used) should be the same as Comer as well. EX1046, ¶177.

6. Claim 6

Nuwayser in view of Comer disclose and suggest the subject matter of claim 6. *See* §VII.B.6 (Ground 1, claim 6). Claim 6 is obvious for the reasons discussed in connection with claim 2. EX1046, ¶178.

7. Claims 7-9

Nuwayser in view of Comer disclose and suggest the subject matter of claims 7-9. *See* §VII.B.7 (Ground 1, claims 7-9). Claims 7-9 are obvious because both Nuwayser and Comer teach monthly dosing and a POSITA would use as many of these same dosage forms as needed throughout the course of treatment. EX1046, ¶179.

8. Claim 10

Nuwayser in view of Comer disclose and suggest the subject matter of claim 10. *See* §VII.B.8 (Ground 1, claim 10). Claim 10 is obvious as Comer and Rubio teach that naltrexone for treatment of alcoholism was safe and effective. EX1046, ¶180.

9. Claim 11

Nuwayser in view of Comer disclose and suggest the subject matter of claim 11. *See* §VII.B.9 (Ground 1, claim 11). Claim 11 requires that the patient not receive an “initial” dose of naltrexone orally. Nothing in Nuwayser discloses giving any prior dose of naltrexone. EX1046, ¶181.

10. Claim 12

Nuwayser in view of Comer disclose and suggest the subject matter of claim 12. *See* §VII.B.10 (Ground 1, claim 12). Claim 12 requires that the parenteral administration be an injection. Nuwayser teaches subcutaneous injection (“SC”)

and therefore discloses claim 12. Comer also discloses administration by injection. EX1046, ¶182.

11. Claim 13

Nuwayser in view of Comer disclose and suggest the subject matter of claim 13. *See* §VII.B.11 (Ground 1, claim 13). While Nuwayser exemplifies a formulation that includes naltrexone in the amount of 54.4% by weight (EX1005, 19:22-23), Wright demonstrates that it was well-known to employ naltrexone drug loading in the range of 30-75% by weight of the formulation. EX1007, 7:63-8:1. *See also id.*, 12:8-32 (disclosing the use of PLGA microparticles). Thus, the claimed naltrexone concentration is encompassed by the range contemplated by the prior art and is not patentable, *e.g.*, given that a POSITA would have had reason to optimize the concentration of the naltrexone formulation in view of the fact that the prior art teaches the general conditions of the Challenged Claims, explained above. EX1046, ¶183.

VIII. OTHER CONSIDERATIONS

A. Any Purported Secondary Considerations Evidence Does Not Overcome the Strong Evidence of the Obviousness of the Claims

All elements of the Challenged Claims are known in the art, and any differences between the Challenged Claims of the '499 Patent and Comer would have been obvious to a POSITA based on the disclosures of the applied references and the knowledge in the art. As explained above in Section VII, the prior art cited

in this Petition demonstrates that it was already known to administer the same amount of naltrexone with the same biocompatible polymer (PLGA) resulting in the purported unexpected result of the serum AUC of naltrexone is about three times greater than that achieved by 50 mg/day oral administration, as that claimed. The purported unexpected results were not only expected, the AUC results were in fact already realized and obtained in the prior art, as explained above. That is, the purported invention of the '499 Patent merely calls for use of a known drug (naltrexone) at a known dose (384 mg) with a known sustained release additive (PLGA), to address the known problem of patient compliance. The serum AUC is merely a predictable result of the combination of known elements, and that too is also expressly disclosed in the prior art. The Challenged Claims are not patentable. EX1046, ¶184.

Any purported evidence of secondary considerations that Patent Owner may present in this proceeding would be insufficient to overcome the strong evidence of obviousness of the Challenged Claims.

B. The Amneal IPR Does Not Warrant Discretionary Denial Under *General Plastic*

As noted above, the '499 Patent was previously challenged in IPR2018-00943 (“the Amneal IPR”) filed by Amneal Pharmaceuticals LLC (“Amneal”). The Board instituted trial of the Amneal IPR. EX1058. Parties subsequently settled and jointly moved to terminate the IPR, and the Board granted the motion. EX1059. Given that

the Amneal IPR was terminated after institution but prior to issuance of a final written decision, serious unresolved questions remain concerning the validity of the Challenged Claims of the '499 Patent. The terminated Amneal IPR constitutes reason to institute trial to resolve these issues in this IPR proceeding, not deny it.

Discretionary denial is unwarranted in view of the factors set forth in *General Plastic Indus. Co., Ltd. v. Canon Kabushiki Kaisha*, IPR2016-01357, Paper 19 (PTAB Sept. 6, 2017) (precedential as to §II.B.4.i). The Petitioner in this IPR proceeding, Apotex, is not the same as the petitioner that requested review in previous IPR2018-00943, Amneal. EX1067, at pp. 1, 61.

Further, Petitioner Apotex does not bear any “significant relationship” with Amneal as articulated in *Valve Corp. v. Electronic Scripting Prods., Inc.*, IPR2019-00062, Paper 11 (PTAB Apr. 2, 2019). In *Valve*, the Board denied institution where the first and second petitioners had a “significant relationship”, *i.e.*, the first and second petitioners were co-defendants in the same district court litigation and accused of infringing the challenged patent based on devices sold by one petitioner that incorporated technology licensed from the other petitioner. *Id.* at 10. No such “significant relationship” exists between Apotex and Amneal. Apotex and Amneal were not co-defendants in a district court litigation. In fact, neither Apotex nor Amneal was accused of infringing any claim of the '499 Patent in any district court litigation, much less based on the same allegedly infringing technology. Nor did

Apotex and Amneal enter into any licensing agreement pertaining to technology accused of infringing any claim of the '499 Patent.

The PTAB may not discretionarily deny institution where different petitioners do not share a “significant relationship”, as is the case here. In *Videndum*, the Director vacated an institution decision exercising discretion to deny a second petition under virtually identical circumstances. *Videndum Prod. Solutions, Inc. v. Rotolight Ltd.*, IPR2023-01218, Paper 12 at 5-6 (PTAB Apr. 19, 2024) (Director Review) (vacating an institution decision exercising discretion to deny a second petition “where, as here, the first and second petitioners are neither the same party, nor possess a significant relationship under *Valve*”). The Director explained that under such circumstances, “*General Plastic* factor one [*i.e.*, whether the same petitioner previously filed a petition directed to the same claims of the same patent] necessarily outweighs the other *General Plastic* factors.” *Id.* at 6. As noted above, the facts in the present case are indistinguishable from *Videndum*. Petitioner Apotex is not the same party as Amneal, nor is Petitioner Apotex a real party-in-interest or privy of Amneal. The Board instituted trial in the Amneal IPR and parties moved to terminate due to settlement on the eve of oral argument—much like the circumstances of the initial IPR proceeding in *Videndum*. There is no “significant relationship” under *Valve* and as such, *General Plastic* factor one outweighs the other factors and discretionary denial is unwarranted. *See Videndum*, IPR2023-

01218, Paper 12 at 6 (“Under USPTO policy and precedent, *General Plastic* has not been extended to any cases in which the first and second petitioners *do not have* a significant relationship.”).

B. The Board Should Not Use Its Discretion to Deny Institution Under *Fintiv*

The Board should decline any request by Patent Owner to exercise discretion to deny institution under 35 U.S.C. §314(a). As an initial matter, there is no currently pending litigation involving the ’499 Patent and Petitioner Apotex. The ’499 Patent was previously involved in a district court litigation (“Teva Litigation”) that settled prior to any final determination concerning invalidity. EX1068. Petitioner Apotex was not even a party to the Teva Litigation. The *Fintiv* factors do not apply to Petitioner Apotex given that the Teva Litigation did not involve Petitioner Apotex and is not even currently pending. *See Apple Inc. v. Fintiv, Inc.*, IPR2020-00019, Paper 11 at 5 (PTAB Mar. 20, 2020) (applying “Factors Related to a Parallel, Co-Pending Proceeding”); *see also Google LLC v. Multimodal Media LLC*, IPR2024-00053, Paper 10 at 6-8 (PTAB Jun. 5, 2024) (determining that “*Fintiv* does not apply to [Petitioner] Google” given that “there is no litigation currently pending against [Petitioner Google]”).

Assuming (incorrectly) that the *Fintiv* factors apply, Factor 6 is dispositive given the compelling evidence of unpatentability set forth in this Petition. *See* USPTO Director’s Memorandum issued on June 21, 2022, titled “Interim Procedure

for Discretionary Denials in AIA Post Grant Proceedings with Parallel District Court Litigation” at p. 2 (“the PTAB will not rely on the *Fintiv* factors to discretionarily deny institution in view of parallel district court litigation where a petition presents compelling evidence of unpatentability.”). The challenges presented in this Petition are particularly compelling given that the Board previously determined that grounds based on the same prior art demonstrated a reasonable likelihood of success and warranted institution (EX1058), as explained above.

Moreover, the Grounds encompass straightforward anticipation and obviousness challenges based on express disclosures and teachings found in the prior art. *See, e.g., Inergy Tech., Inc. v. Force Mos Tech., Co., Ltd.*, IPR2024-00094, Paper 9 (PTAB May 21, 2024) at p. 36 (finding compelling merits where the obviousness ground is “seemingly straightforward” and “Petitioner’s motivation for this modification comes from an express teaching in [the cited reference]”). None of the grounds asserted herein were ultimately resolved by either the Office or the district courts, also favoring institution. *See Comcast Cable Comm’n’s, LLC v. Rovi Guides, Inc.*, IPR2019-00231, Paper 14 at 11 (PTAB May 20, 2019) (obviousness challenges not “previously considered by the Office or any court” weigh in favor of not denying institution).

C. The Board Should Not Use Its Discretion to Deny Institution Under Section 325(d)

Comer was made of record but not substantively discussed or applied in a rejection by the Patent Office during prosecution. Nuwayser was not made of record, much less substantively treated by the Patent Office. Accordingly, discretionary denial under Section 325(d) is unwarranted.

The *Becton, Dickinson* factors weigh in favor of institution. The Patent Office's lack of substantive treatment of Comer constitutes "material error" under *Advanced Bionics* because the Patent Office overlooked the disclosures of such references that impact patentability of the Challenged Claims. The Board has consistently declined to discretionarily deny institution under similar facts. *See, e.g., DISH Network LLC v. Sound View Innovations, LLC*, IPR2020-01041, Paper 13, 22 (PTAB Jan 19, 2021); *Roku, Inc. v. Universal Electronics, Inc.*, IPR2019-01615 (PTAB April 17, 2020); *Trans Ova Genetics, LC v. XY, LLC*, IPR2018-00250, Paper 9, 18-19 (PTAB June 27, 2018).

The grounds in this Petition substantially differ from the issues considered during prosecution. According to the Examiner, Tice (EX1009) was the closest prior art and reported that its injectable formulation was comparable to taking 50 mg tablets orally. EX1002, at 111-112. But, as discussed above, Tice is not the closest prior art. Comer discloses and suggests the claimed "about 310 mg to about 480 mg" recitation that secured allowance. *See* §VII.

In the Amneal IPR, the Board previously determined that denial was unwarranted given the lack of evidence concerning the extent of the treatment of Comer during prosecution, and the same is true here. EX1058, at p. 40 (“Although Comer is listed on the face of the ’499 patent, we have no evidence about the extent to which the Examiner evaluated Comer during examination.”). The fact that Comer was merely made of record during prosecution does not warrant discretionary denial.

With respect to *Becton Dickinson* factor (f), the Petition is supported by an expert declaration by Dr. Dowling explaining how a POSITA would have understood Comer and Nuwayser. *See, e.g.*, EX1046, ¶¶20-24. This new evidence also weighs against discretionary denial. *See, e.g., Puma N. Am., Inc. v. Nike, Inc.*, IPR2019-01058, Paper 10, 19 (PTAB Oct. 31, 2019) (instituting where petition presented “new noncumulative evidence ... probative to issues of patentability and helpful to our consideration of a prior art combination that was not before the Examiner”).

IX. CONCLUSION

For at least the foregoing reasons, Claims 1-13 of the ’499 Patent are unpatentable. Since Petitioner has shown the claims to be *prima facie* obvious, Petitioner has also shown a likelihood of success on the merits. Therefore, this Petition should be granted, and the Board should institute trial.

Petition for *Inter Partes* Review of U.S. Patent No. 7,919,499

Date: January 30, 2025

Respectfully submitted,

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Appendix A

Naltrexone AUC calculations based on 384 mg IM dose

$$\text{AUC}_{1-n} = \sum \left\{ \frac{Cp_1 + Cp_2}{2} \cdot (t_2 - t_1) \right\} + \left\{ \frac{Cp_2 + Cp_3}{2} \cdot (t_3 - t_2) \right\} + \dots$$

Table 1: Adapted from Comer (Figure 1)

Time (Day)	Measured from Y axis (mm)	Mean Conc from plot (Cp, ng/mL)	AUC* (ng·day/mL)	AUC interval (in days)
0	0	0		
0.08333333 (2 hours)	43	8.9	0.37	0-0.083
1	38	7.9	7.68	0.083-1
2	34	7.0	7.45	1-2
3	26	5.4	6.21	2-3
4	24	5.0	5.17	3-4
5	19	3.9	4.45	4-5
6	18	3.7	3.83	5-6
8	19	3.9	7.66	6-8
11	25	5.2	13.66	8-11
15	17	3.5	17.39	11-15
18	15	3.1	9.93	15-18
22	11	2.3	10.76	18-22
25	7.5	1.6	5.74	22-25
28	5	1.0	3.88	25-28
			104.20	0-28

Oral Naltrexone 50 mg/d (AUC₀₋₂₈) = 35.78

Ratio differential: Comer 384 mg IM dose AUC₁₋₂₈ : 50 mg/d AUC₀₋₂₈
104.20 : 35.78

2.9

APPENDIX B—LIST OF EXHIBITS

EXHIBIT	DESCRIPTION
1001	U.S. Patent No. 7,919,499, issued on April 5, 2011 to E. Ehrich (“the ’499 Patent”)
1002	File History of U.S. Patent Application No. 11/083,167, filed on March 17, 2005 (“the ’167 Application”)
1003	U.S. Provisional Application No. 60/564,542, filed on April 22, 2004
1004	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
1005	U.S. Patent No. 7,157,102, issued on January 2, 2007 to E. Nuwayser (“the ’102 Patent” or “Nuwayser”)
1006	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
1007	U.S. Patent No. 6,264,987, issued on July 24, 2001 to S. Wright <i>et al.</i> (“the ’987 Patent” or “Wright”)
1008	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
1009	U.S. Patent No. 6,306,425, issued on October 23, 2001 to T. Tice <i>et al.</i> (“Tice”)
1010	C.N. Chiang <i>et al.</i> , <i>Clinical Evaluation of A Naltrexone Sustained-Release Preparation</i> , 16 <i>Drug & Alcohol Dependence</i> (1985), at 1-8

EXHIBIT	DESCRIPTION
1011	T.N. Alim <i>et al.</i> , <i>Tolerability Study of A Depot Form of Naltrexone Substance Abusers</i> , Problems of Drug Dependence, 1994: Proceedings of the 56th Annual Scientific Meeting, The College on Problems of Drug Dependence, Inc., Vol. II: Abstracts, National Institute on Drug Abuse Research Monograph 153 (1995), at 253
1012	U.S. Securities and Exchange Commission, <i>FORM 10-K, Annual Report Pursuant to Section 13 or 15(d) of the Securities Exchange Act of 1934 for the fiscal year ended March 31, 2002</i> . Alkermes, Inc. (July 2002)
1013	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”)
1014	S.J. Heishman <i>et al.</i> , <i>Safety And Pharmacokinetics of a New Formulation of Depot Naltrexone</i> , Problems of Drug Dependence, 1993: Proceedings of the 55th Annual Scientific Meeting, The College on Problems of Drug Dependence, Inc., Volume II: Abstracts, National Institute on Drug Abuse Research Monograph 141 (1994)
1015	U.S. Patent and Trademark Office, 1265(2) <i>Official Gazette of the United States Patent and Trademark Office</i> , Trademarks, Dec. 10, 2002
1016	Stewart B. Leavitt, PhD, ed., <i>Evidence for the Efficacy of Naltrexone in the Treatment of Alcohol Dependence (Alcoholism)</i> , Addition Treatment Forum Naltrexone Clinical Update (2002 Clinco Communications, Inc.), at 1-8
1017	ReVia, <i>Physicians’ Desk Reference</i> 936-938 (53rd ed. 1999) (“PDR”)
1018	U.S. Patent No. 4,882,335, issued on November 21, 1989 to J. Sinclair (“Sinclair”)

Petition for *Inter Partes* Review of U.S. Patent No. 7,919,499

EXHIBIT	DESCRIPTION
1019	Chiang <i>et al.</i> , <i>Kinetics of a naltrexone sustained-release preparation</i> , 36(5) Clin. Pharmacol. Ther. (Nov. 1984), at 704-08 “Kinetic of a naltrexone sustained-release preparation.”
1020	Reuning <i>et al.</i> , <i>Pharmacokinetic Quantitation of Naltrexone Release From Several Sustained-Release Delivery Systems</i> , Naltrexone: Research Monograph 28 (R. E. Willette and G. Barnett, eds. National Institute on Drug Abuse 1980)
1021	Appeal Brief, Application No. 13/871,534, Oct. 19, 2015
1022	<i>Not assigned</i>
1023	<i>Not assigned</i>
1024	<i>Not assigned</i>
1025	<i>Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations</i> , Product Details for NDA 018932, REVIA (NALTREXONE HYDROCHLORIDE) 50MG
1026	<i>Not assigned</i>
1027	<i>Not assigned</i>
1028	<i>Not assigned</i>
1029	TREXAN™, <i>Physicians’ Desk Reference</i> 936-938 (46 ed. 1992) (“PDR”), at 937-939
1030	<i>Trademark Manual of Examining Procedure (TMEP)</i> (3rd ed. Jan. 2002), at 100-5 to 100-11
1031	<i>Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations</i> , NALTREXONE (VIVITROL) FOR SUSPENSION, EXTENDED RELEASE 380MG/VIAL
1032	<i>Not assigned</i>

EXHIBIT	DESCRIPTION
1033	Bertil Abrahamsson and Anna-Lena Ungell, <i>Biopharmaceutical support in formulation development: A Practical Guide from Candidate Drug Selection to Commercial Dosage Form</i> , Pharmaceutical Preformulation and Formulation (Mark Gibson ed., Interpharm/CRC) (2004), 239-291, at 262
1034	Guidance for Industry. Bioavailability and Bioequivalence Studies for Orally Administered Products—General Considerations. FDA CDER (March 2003)
1035	Riddle <i>et al.</i> , <i>Anxiolytics, adrenergic agents, and naltrexone</i> , 38(5) J. Am. Acad. Child. Adolesc. Psychiatry, 546-556 (May 1999)
1036	<i>Not assigned</i>
1037	Rothenberg <i>et al.</i> , <i>Behavioral naltrexone therapy: an integrated treatment for opiate dependence</i> , 23 J. of Substance Abuse Treatment (2002), at 351-360
1038	B.A. Johnson, <i>Naltrexone long-acting formulation in the treatment of alcohol dependence</i> , 3(5) Ther. Clin. Risk Manag., 741-749 (2007), at 742.
1039	Food and Drug Administration, Guidance for Industry, <i>Exposure-response relationships – study design, data analysis, and regulatory applications</i> , FDA CDER (April 2003)
1040	Food and Drug Administration, Guidance for Industry, <i>Statistical approaches to establishing bioequivalence</i> , FDA CDER (April 2003)
1041	Schenker <i>et al.</i> , <i>Antecedent liver disease and drug toxicity</i> , 31 J. of Hepatology 1098-1105 (1999)
1042	U.S. Patent No. 3,332,950, issued on July 25, 1997 to H. Blumberg
1043	<i>Not assigned</i>

Petition for *Inter Partes* Review of U.S. Patent No. 7,919,499

EXHIBIT	DESCRIPTION
1044	<i>Not assigned</i>
1045	<i>Not assigned</i>
1046	Declaration of Thomas Dowling
1047	<i>Curriculum Vitae</i> of Thomas Dowling
1048	Declaration of Jason Schiffman
1049	<i>Curriculum Vitae</i> of Jason Schiffman
1050	Declaration of June Munford
1051	<i>Curriculum Vitae</i> of June Munford
1052	Resume of Mike Ramstack, as obtained from LinkedIn
1053	Resume of Richard Reuning, as obtained from LinkedIn
1054	Resume of Steve Wright, as obtained from LinkedIn
1055	Declaration Under 37 C.F.R. §1.132 of Elliot Ehrich filed in Application No. Serial No. 11/083,167
1056	S. Hamilton <i>et al.</i> , <i>Pharmacokinetics and Pharmacodynamics of Hyaluronan Infused Healthy Human Volunteers</i> , 3 The Open Drug Metabolism Journal 43-55 (2009)
1057	Trademark Registration No. 2,443,435 (Depotrex)
1058	Institution Decision entered November 7, 2018 (Paper 8) in IPR2018-00943
1059	Termination Decision entered July 31, 2019 (Paper 29) in IPR2018-00943
1060	Patent Owner's Response, filed February 7, 2019 (Paper 14) in IPR2018-00943

Petition for *Inter Partes* Review of U.S. Patent No. 7,919,499

EXHIBIT	DESCRIPTION
1061	U.S. Patent No. 5,210,083, issued on May 11, 1993 to R. Pfirrmann
1062	U.S. Patent No. 5,234,906, issued on August 10, 1993 to A. Young and G. Cooper
1063	U.S. Patent No. 6,677,320, issued on January 13, 2004 to A. Diederich <i>et al.</i>
1064	U.S. Patent No. 6,120,787, issued on September 19, 2000 to N.O. Gustafsson <i>et al.</i>
1065	U.S. Patent Publication No. 2003/0211167, published on November 13, 2003
1066	U.S. Patent No. 6,455,526, issued on September 24, 2002 to R. Kohn <i>et al.</i>
1067	Petition for Inter Partes Review of U.S. Patent No. 7,919,499, IPR2018-00943, filed on April 20, 2018
1068	Stipulated Consent Judgment and Injunction, filed August 30, 2023 in <i>Alkermes v. Teva Pharmaceuticals</i> , Civ. Action No. 2:20-cv-12470 (DNJ)

CERTIFICATE OF COMPLIANCE WITH 37 C.F.R. §42.24

I hereby certify that the word count for the foregoing Petition totals 13,987 words, excluding the parts which are exempted by 37 C.F.R. §42.24(a)(1).

Date: January 30, 2025

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CERTIFICATE OF SERVICE

The undersigned hereby certifies that on this 30th day of January, 2025, a true and correct copy of the foregoing **PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 7,919,499** and **EXHIBITS 1001–1021, 1025, 1029-1031, 1033-1035, 1037-1042, 1046-1068** are being served by UPS on the correspondence address of record as follows:

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