

Case IPR2018-00943
Patent No. 7,919,499
Petition for *Inter Partes* Review
Attorney Docket No. AMNEAL 7.1R-005

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AMNEAL PHARMACEUTICALS LLC,
Petitioner,

v.

ALKERMES PHARMA IRELAND LIMITED,

Patent Owner.

Patent No. 7,919,499 to Elliot Ehrich
Issue Date: May 19, 2015
Title: NALTREXONE LONG ACTING
FORMULATIONS AND METHODS OF USE

Inter Partes Review No. IPR2018-00943

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

APOTEX EXHIBIT 1067
Apotex v. Alkermes
IPR2025-00514

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1001	U.S. Patent No. 7,919,499 (“the ’499 Patent”)
1002	U.S. Serial Number 11/083,167, Office Action, May 5, 2009
1003	Serial No. 11/083,167, Declaration Under 37 C.F.R. § 1.132 of Elliot Ehrich (undated)
1004	U.S. Serial Number 11/083,167, Amendment and Response, Oct. 5, 2009
1005	U.S. Serial Number 11/083,167, Office Action, Jan. 6, 2010
1006	U.S. Serial Number 11/083,167, Amendment and Response, Apr. 5, 2010
1007	U.S. Serial Number 11/083,167, Final Rejection, July 20, 2010
1008	U.S. Serial Number 11/083,167, Amendment After Final, Oct. 20, 2010
1009	U.S. Serial Number 11/083,167, Notice of Allowance, Dec. 1, 2010
1010	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
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1013	T.N. Alim <i>et al.</i> , <i>Tolerability Study of A Depot Form of Naltrexone Substance Abusers</i> , <i>Problems of Drug Dependence</i> , 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
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1018	U.S. Patent No. 6,264,987 (“the ’987 Patent” or “Wright”)
1019	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)
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1023	ReVia, <i>Physicians’ Desk Reference</i> 936-938 (53rd ed. 1999) (“PDR”)
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1025	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.”
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1033	Manit Srisurapanont & Ngamwong Jarusuraisin, <i>Naltrexone for the treatment of alcoholism: a meta-analysis of randomized controlled trials</i> , 8 Int'l J. of Neuropsychopharmacology (2005), at 267-280
1034	Bouza Carmen <i>et al.</i> , <i>Efficacy and safety of naltrexone and acamprosate in the treatment of alcohol dependence: a systematic review</i> , 99(7) Addiction (July 2004), at 811-828
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1038	Synopsis, Naltrexone HCl, ALZA Corporation (Nov. 3, 2003)
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1040	TREXAN™, <i>Physicians' Desk Reference</i> 936-938 (46 ed. 1992) ("PDR"), at 937-939
1041	<i>Trademark Manual of Examining Procedure (TMEP)</i> (3rd ed. Jan. 2002), at 100-5 to 100-11
1042	<i>Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations</i> , NALTREXONE (VIVITROL) FOR SUSPENSION, EXTENDED RELEASE 380MG/VIAL
1043	General Notices and Requirements, USP 32/NF 27 (2009) at 8
1044	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

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1053	Schenker <i>et al.</i> , <i>Antecedent liver disease and drug toxicity</i> , 31 J. of Hepatology 1098-1105 (1999)
1054	Résumé of Mike Ramstack, as obtained from LinkedIn
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1056	Résumé of Steve Wright, as obtained from LinkedIn
1057	U.S. Patent No. 3,332,950
1058	Filing Details for Alkermes Inc. 10-K dated July 1, 2002 from the Security and Exchange Commission’s EDGAR Online Filing System
1059	WayBack Machine capture of Security and Exchange Commission’s Information Page regarding the Electronic Data Gathering, Analysis, and Retrieval System (EDGAR), June 6, 2002
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Pursuant to 35 U.S.C. §§ 311-319 and 37 C.F.R. § 42, Amneal Pharmaceuticals LLC (“Amneal” or “Petitioner”) petitions for *Inter Partes* Review (“IPR”) seeking cancellation of claims 1-13 (“the challenged claims”) of U.S. Patent No. 7,919,499 (“the ’499 Patent”) (Ex. 1001). The Statement of Precise Relief Requested and Mandatory Notices follow the Conclusion of this Petition.

I. OVERVIEW

The ’499 Patent claims a method of treating alcoholics, among others, using 310-480 mg of parenterally-administered naltrexone in a long-acting formulation comprising the biocompatible polymer polylactide-co-glycolide (“PLGA”), also known as poly(lactic-co-glycolic acid). According to Patent Owner Alkermes Pharma Ireland Limited (“Alkermes”), the alleged invention resides in an “unexpected discovery” made during clinical trials that its 380 mg naltrexone formulation provided a greater area under the curve (“AUC”) than resulted from 50 mg/day oral administration. (Exs. 1001 Abstract, 1:31-33; 21:6-7; 1003, at 1.)

In reality, Alkermes’ AUC “discovery” argument is flawed, inconsequential, and irrelevant. It is flawed because comparisons made to oral naltrexone treatments, and even those made during prosecution to the depot injection formulation of Tice (Ex. 1015), are not comparisons to the closest prior art. The closest prior art actually includes identical PLGA formulations containing about 380 mg of naltrexone, administered in monthly depot injections.

The “discovery” is inconsequential because it is not linked to any meaningful improvement in therapeutic efficacy. Alkermes had ample motive and opportunity to establish superior efficacy, if it could, but chose not to do so. Perhaps that is because the preponderance of the evidence, in fact, suggests that any way of maintaining therapeutic blood levels of naltrexone of at least 1 ng/ml will be effective. And 50 mg/day oral administration did just that. Whether that AUC is a fraction of that resulting from some other dose or protocol, or multiples of it, is quite beside the point.

Finally Alkermes’ “discovery” is irrelevant. Alkermes 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.

This assumes, however, that the same oral data is used for the comparison. Alkermes presented no data in its specification, either for the AUC of its protocol or for 50 mg/daily oral dosing, making the analysis of any AUC differential a moving target. Using some, but not all, available oral data will result in the claimed AUC differential. Alkermes also never explained that no matter what the AUC

differential is, there is no established meaningful effect on performance—whether AUC was equal to that of oral, or 50 times greater. Because AUC is dependent on dose, as Alkermes admitted, and the art dosed the same amount of the same drug from the same vehicle on the same protocol, it must result in the same or at least highly similar AUCs and differentials. The resulting AUC of its parenteral formulation compared to some other protocol might be interesting, but it is certainly not a credible reason to grant a patent. 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.

Admittedly, the discovery of a new property of any known or obvious product can be the basis of patentability *when a new method results from that discovery*. But here the method merely resulted *in* the discovery; the discovery did not lead to some unobvious change in a method. The claimed method is not new or unobvious.

**II. IDENTIFICATION OF THE CLAIMS
BEING CHALLENGE (37 C.F.R. § 104(b))**

The Board should find the challenged claims unpatentable on the following grounds:

Ground	35 U.S.C.	Claims	References
1	102(b)	1, 3-5, 10-12	Comer
2	102(b)	1, 3-5, 11, 12	Nuwayser
3	103(a)	All challenged claims	Comer in view of Nuwayser, Rubio, and Wright
4	103(a)	All challenged claims	Nuwayser in view of Comer, Rubio, and Wright
5	103(a)	All challenged claims	Nuwayser in view of Kranzler, Rubio, and Wright
6	103(a)	All challenged claims	Alkermes' 10-K in view of the Vivitrex Specimen Wright, and Rubio

A copy of each reference is filed herewith. The grounds for unpatentability are supported by the Declaration of Kinam Park, Ph.D. (Exs. 1030; 1031.)

III. SUMMARY OF THE ARGUMENT

First, claims 1, 3-5, and 10-12 are anticipated by Comer (Ex. 1010), as evidenced by Nuwayser (Ex. 1014) (Ground 1). Comer describes each element claimed, including the allegedly unexpected AUC. Nuwayser evidences what a POSA would understand from Comer's reference to "Depotrex."

Second, claims 1, 3-5, and 11-12 are anticipated by Nuwayser (Ground 2), which similarly describes each element claimed and discloses the claimed dose to a POSA by integration of the blood level plot in Figure 7.

Next, all of the challenged claims are obvious over Comer in view of Nuwayser, Rubio (Ex. 1028), and Wright (Ex. 1018) (Ground 3); and Nuwayser in view of Comer, Rubio, and Wright (Ground 4). Comer does not discuss the specifics of the Depotrex formulation used. But a POSA interested in Depotrex would find Nuwayser, which describes it fully. Taken from the opposite direction, 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 POSA would find Comer, which used the same protocol, resulting in an identical plasma level plot, and used about 380 mg of Depotrex to do so.

The challenged claims are also obvious in view of Nuwayser in view of Kranzler (Ex. 1011), Rubio, and Wright (Ground 5). As Dr. Park explains, it would be obvious to establish a dose using a standard curve. (Ex. 1030 ¶¶ 116-117.) Rubio and Wright are applicable to dependent claims 2, 6, and 13 in Grounds 3-5.

Finally, all of the challenged claims are obvious over Alkermes' 10-K (Ex. 1016) in view of the Vivitrex[®] Trademark Specimen (Ex. 1017), Rubio, and

Wright (Ex. 1018) (Ground 6). Alkermes' 10-K describes the claimed method and the use of Alkermes' Vivitrex depot injection of naltrexone and Medisorb[®] technology to treat alcoholism—and opioid addicts. The Specimen confirms the use of its Medisorb technology with naltrexone and provides the dose found in Vivitrex. Wright fully describes the Medisorb microparticles. The result, in terms of AUC and differential, should be the same as claimed because this ground is based on the use of the very same formulation used by Alkermes in the claimed study described in the '499 Patent. Wright and Rubio are also applicable to dependent claims 2, 6, and 13.

IV. SUMMARY OF THE '499 PATENT

The '499 Patent (Ex. 1001)¹ issued on April 5, 2011, from U.S. Application Serial No. 11/083,167 (“the '167 Application”), filed on March 17, 2005, and claims the benefit of U.S. Provisional Application No. 60/564,542, filed April 22, 2004 (the “Provisional Application”) (Ex. 1032.) Accordingly, the earliest possible effective filing date for the '499 Patent is April 22, 2004.

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

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

naltrexone is about three times greater than what is achieved by administration of 50 mg/day oral administration. (Ex. 1001, 1:30-46.)

The '499 Patent alleges that the “inventions described herein arose from unexpected discoveries made during clinical trials with a long acting formulation of naltrexone.” (Exs. 1001 Abstract, 1:31-33; 1030 ¶ 15.) It provides no direct data for the AUC of any claimed formulation or the comparator—50 mg/day oral dosing. (Ex. 1001, 18:10-12; 1030 ¶ 15.) During prosecution, comparisons were made using data from an Alkermes’ study referenced in the '499 Patent and from Tice. (Exs. 1003; 1015.) But none of this data could be determined from the patent itself.

The specification discusses the need for improving naltrexone therapies, based on patient compliance. (Exs. 1001, 1:13-26, 17:24-29; 1030 ¶ 16.) In some embodiments, the naltrexone is combined with well-known polymers, such as PLGA, to “entrap or encapsulate” the naltrexone and provide a long-acting formulation. (Exs. 1001, 3:14-15; 1030 ¶ 17.)

The specification describes its long-acting formulations as releasing naltrexone over a period of at least one week. (Ex. 1001, 3:59-64, 4:42-44.) It then describes “Vivitrex” as a monthly administration that releases naltrexone for four weeks, and that the therapy can be maintained for 24 weeks or more. (*Id.* 4:54-64.)

Five examples are included, three of which (Examples 3-5) were not present in the provisional application. (*Compare* Exs. 1001 and 1032; 1030 ¶ 18.) 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* Exs. 1001, 3:3-33, 5:35-8:2 and 1018, 7:50-8:60; 1030 ¶¶ 132-133.) The remaining examples describe various aspects of a clinical trial and meta-analysis. Example 2 describes screening, eligibility, and adverse events. (Ex. 1001, 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.*” (Exs. 1001, 18:10-12 (emphases added); 1030 ¶¶ 19, 61.) 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 POSA to mean comparable or equivalent to, as the ’499 Patent’s data would not establish improved efficacy to a POSA. (Exs. 1030 ¶¶ 16, 61; 1001, 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.

V. PERTINENT PROSECUTION HISTORY OF THE '499 PATENT

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.

A nonfinal rejection was mailed on May 5, 2009 (Ex. 1002), which rejected the claims as allegedly being anticipated by Tice and, in the alternative, as being obvious over the combination of Tice and Chandrashekar. Alkermes responded on October 5, 2009 (Ex. 1004), with claim amendments and a declaration under 37 C.F.R. § 1.132 by Elliot Ehrich (the “Ehrich Declaration” (Ex. 1003)), 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. (Ex. 1030 ¶¶ 23, 63, 72-74.)

The Examiner issued a second office action on January 6, 2010, which withdrew the anticipation and obviousness rejections over Tice in view of the Ehrich Declaration but nevertheless rejected the claims for lack of enablement.

(Ex. 1005.) Alkermes responded on April 5, 2010, by amending the claims to require a biocompatible polymer. (Ex. 1006.) A final rejection was mailed on July 20, 2010, maintaining the enablement rejection. (Ex. 1007.) Alkermes filed a response after final on October 20, 2010, amending the claims further to require that the biocompatible polymer be PLGA. (Exs. 1008; 1030 ¶ 23.)

A Notice of Allowance was mailed on December 1, 2010, which acknowledged a telephone interview of November 19, 2010, where Alkermes agreed to an Examiner's Amendment to insert certain language into the claims, *e.g.*, "about 310 mg to about 480 mg" into claim 1. (Ex. 1009.) The Examiner also included reasons for allowance. According to the Examiner, Tice was the closest prior art and reported that its injectable formulation was comparable to taking 50 mg tablets orally. (*Id.*) But, as discussed below, Tice is not the closest prior art. (Ex. 1030 ¶ 24.)

VI. TECHNICAL BACKGROUND AND STATE OF THE ART

The challenged claims are directed to treating certain conditions, such as alcoholism. Naltrexone as a treatment for patients suffering from alcoholism and opioid addiction dates back to at least the 1980s. (Exs. 1010, at 351-352; 1011, at 1075; 1012 Summary; 1013; 1014, 19:22-25; 1016, at 3; 1022 Abstract; 1023, at 936; 2024, 1:55-2:50; 1026, at 173; 1030 ¶¶ 52-53.) Indeed, naltrexone in an amount of 50 mg/day delivered orally was a known effective treatment since at

least November 20, 1984. (Exs. 1012, at 354; 1019; 1022, at 2; 1023, at 936-938; 1028, at 420; 1030 ¶ 52.) It was known to provide serum blood levels of at least 1 ng/ml, which was recognized as necessary for therapeutic efficacy. (Exs. 1010 Abstract; 1011, at 1078; 1012, at 7; 1015, 6:19-39; 1019; 1025, at 708; 1030 ¶ 52.)

One of the most frequently cited problems with treating these types of patients was patient compliance, and one of the most oft-cited ways to address compliance was the use of long-acting depot injections. (Exs. 1010, at 351-352, 1011, at 1075; 1012, at 2; 1013; 1015, 1:46-2:7; 1019; 1025, at 704; 1030 ¶ 54.) Several depot formulations of naltrexone were known to provide at least the 1 ng/ml serum levels for weeks. (Exs. 1010, at 351; 1011, at 1078; 1014 Fig. 7; 1015, 3:5-17, 4:35-39, 6:15-39; 1030 ¶ 54.) These depot formulations included naltrexone and PLGA. (Exs. 1010, at 354; 1011, at 1075; 1012, at 2; 1014, 14:24-49, 19:4-25; 1018, 7:50-8:60, 12:33-40; 1025, at 704; 1026, at 173 (delivery system I); 1030 ¶ 55.) Administering naltrexone doses falling within the claimed range of about 310 mg to about 480 mg from such PLGA-containing formulations was also known. (Exs. 1010, at 351, 7; 1014, 19:4-25, Fig. 7; 1017, at 3, 15; 1030 ¶ 55.)

Other than the claimed AUC differential, all elements of the '499 Patent were known. And, as described herein, the claimed AUC differential was also known. (Ex. 1030 ¶ 55.) Allegedly, Alkermes' formulation unexpectedly provided

an AUC that was about three times greater than that achieved by 50 mg/day of oral administration (the “AUC differential” or “differential”). But this AUC differential, even if true—which, for the reasons discussed herein, is highly questionable—should not support patentability. A method of medical treatment is claimed. Whether the AUC of the claimed formulation is the same or several times that resulting from daily oral dosing makes no meaningful therapeutic difference. Any of the prior art formulations that provide at least 1 ng/ml/day serum levels should be therapeutically effective (if used correctly). (Ex. 1030 ¶¶ 54, 60.) During prosecution, Alkermes distinguished Tice (Ex. 1015) by arguing that Tice’s depot injection of up to 350 mg of naltrexone resulted in an AUC that was only about the same as oral dosing. (Ex. 1003, at 4.) Alkermes did not, however, argue that either Tice, or oral dosing, were less effective than the method claimed. Merely observing an interesting pharmacokinetic property, offering no practical advantage, should not be enough to patentably distinguish the art.

Moreover, having made AUC the distinguishing feature of its claims, Alkermes provides a shocking lack of information to establish the existence of the claimed AUC differential. The ’499 Patent merely states that the AUC of its formulation will be a multiple of the AUC from 50 mg/day oral dosing. (Ex. 1001, 1:36-39, 2:25-36.) But it provides no direct data whatsoever, or even a reference to oral data usable for the comparison. It provides no data to show that the claimed

result is ever realized, let alone across the entire broad range of 310-480 mg. Since Alkermes acknowledges that AUC is dose-dependent, the AUC and its differential should vary widely across the claimed range. And, as Dr. Park notes, the data used for the comparison can directly impact whether the claimed AUC difference is realized. (Ex. 1030 ¶¶ 81-86.)

Finally, the comparisons made in the claims and in the Ehrich Declaration were not made to the closest prior art. (*Id.* ¶¶ 24, 63.) Neither oral dosing nor the PLA depot injection of Tice (Ex. 1015), the only two technologies to which Alkermes made comparisons, are as close as the prior art depot formulations of Vivitrex™ or Depotrex™. Both of these technologies include one month depot injections of PLGA and about 380 mg naltrexone (squarely in the claimed range). This is the comparison that logically and legally should have been made—but was not.

Because the doses are the same and AUC is dose-dependent, the resulting AUC and differential from Depotrex and Vivitrex formulations should be the same also, assuming the same oral data is used. Indeed, Vivitrex is the same formulation used by Alkermes in its study in the Ehrich Declaration to establish the AUC differential. (Ex. 1030 ¶¶ 67-81.)

One must keep clear the distinctions between AUC and AUC differential. The formulations of Comer, Nuwayser, Vivitrex 10-K and that used in the study of

the '499 Patent all provided the same dose of the same drug delivered from the same formulation, in the same way, to the same patients. And, as noted, Dr. Park and Alkermes appear to agree that pharmacokinetic properties (which include AUC) in this system are dose-dependent. (Exs. 1027, at 7; 1030 ¶¶ 44, 60-62, 70, 78, 81.) Accordingly, since all formulations deliver the same dose of the same drug in the same way, their AUCs *per se* should be an inherent property and should all be the same—or at least not unobviously different from each other.

However, unlike the AUC, which is a pharmacokinetic property that can be directly determined, the claimed AUC *differential* is computational. The AUC differential requires mathematical manipulation using data from 50 mg/day oral dosing. If, as Alkermes did in the Ehrich Declaration, the oral data of Tice or its own data is used, the AUC differentials from Comer, Nuwayser, the Vivitrex 10-K formulation, and the tested formulation of the '499 Patent would all be about three, indeed, about 3.3. (Ex. 1030 ¶¶ 66-81.) If other published oral data were used, none of these formulations would produce that claimed differential. (*Id.* ¶¶ 82-86.) Because the '499 Patent does not specify what oral data to use, the AUC differentials can vary widely. Thus while AUC might be inherent, the AUC differential cannot. But even if the differential were nowhere near about three, a POSA would still consider the claims anticipated or obvious given that the steps,

formulations, and treatments are all the same and the differential in not impactful on efficacy.

Indeed, to the extent that the AUC and differential were not the same, it would either be obvious to adjust the doses so as to arrive at the claimed AUC differential or to consider any difference in AUC differential to be not probative of nonobviousness. AUC differential was not meaningfully linked to efficacy, was predicted on an inapt and improper comparison, and is subject to manipulation based on the data used. Accordingly, any difference in AUC differential would be highly discounted by a POSA. But, as established herein, the prior art does indeed provide an AUC differential of about three when comparing depot injections to 50 mg/day oral dosing when measured against the same oral data used by Alkermes. The claimed AUC difference, to the extent it exists, was known, was not unobvious, and was not a superior result. (*Id.* ¶¶ 16, 61, 81, 86, 103, 106-107, 118, 134.)

VII. PERSON OF SKILL IN THE ART

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

As explained in the Park Declaration, while the claims here are to a method of medical treatment, all of the elements of that method are well documented in the art and understandable by anyone with at least a college education. All of the discussion of patentability during prosecution related to pharmacokinetics, which is ordinarily the province of Pharm.Ds and Ph.Ds in pharmaceuticals and related formulation sciences. Dr. Park opines that a POSA would have such a doctorate level degree in one of these disciplines and at least two years of experience in controlled release formulation. A lesser degree of formal education balanced by additional practical experience could also qualify as a POSA. (Ex. 1030 ¶¶ 28-31.)

VIII. CLAIM CONSTRUCTION

In IPR, a claim term is given its “broadest reasonable construction in light of the specification....” 37 C.F.R. § 42.100(b); *see also* *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2142 (2016).

A. “a long acting formulation”

The claims require a “long acting” formulation. The ’499 Patent states that “long acting” may also be referred to as “extended, sustained, or controlled release” preparations and defines “long acting” as delivering “therapeutically beneficial amounts of naltrexone to a patient for a period of at least one week.” (Ex. 1001, 3:11-13, 3:59-64; 1030 ¶ 34.)

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

The claims require a “serum AUC” but “serum AUC” is not defined by the specification. A POSA would appreciate that this refers to serum “area under the curve.” As Dr. Park explains, a POSA would clearly know the meaning of AUC and how it is determined. (Ex. 1030 ¶¶ 36, 37, 56-59.) But briefly, AUC is merely the area under a curve created by plotting plasma drug concentration versus time. (See, for example, *id.* ¶¶ 38, 56, 69, 73.) As Dr. Park explains, so long as the minimum therapeutic blood levels are maintained, the treatment will be effective regardless of AUC. (*Id.* ¶¶ 38, 60.) Indeed, a higher AUC could indicate unnecessary exposure to the drug. (*Id.* ¶ 60.)

The '499 Patent also lacks a definition of “about three times greater than that achieved by 50 mg/day oral administration,” found in the claims. The problem here is not with the literal wording but with the fact that no data is provided in the specification to establish the AUC of the claimed formulation or the AUC of 50 mg/day oral dosing used for comparison. Instead, the '499 Patent merely makes unsubstantiated assertions about this relationship. (Ex. 1001, 1:36-40, 2:23-36; 1030 ¶¶ 35-47.)

As the '499 Patent does not define or specify the AUC of the claimed formulation or oral dosing, a POSA must look to the art. A POSA would find,

however, that there is no single accepted data set, particularly for the AUC resulting from administering 50 mg/day orally. As Dr. Park explains, the art reports varying data sets for oral dosing, none of which is consistent. (Ex. 1030 ¶¶ 41, 81-86.) And the AUC differential between the claimed formulation and that of oral dosing can be dramatically influenced by which prior art data set is used for oral dosing. (*Id.*) If the AUC data reported in Comer (Ex. 1010) and Nuwayser (Ex. 1014) are compared with the oral AUC data used in the Ehrich Declaration (Ex. 1003), the resulting differential is about three times as claimed. (Ex. 1030 ¶¶ 66-77, 81, 89, 96.) The same result would come from the use of the Tice oral data. (*Id.*) On the other hand, using the data reported in Comer and Nuwayser for their depot injection against other published data for 50 mg/day oral dosing would result in an AUC differential (AUC_{0-28d}), which could be as low as 2.1 or as high as 5.3 times that of oral dosing. (*Id.* ¶¶ 82-86.)

The lack of clarity due to Alkermes' failure to define the AUC of either the claimed formulation or oral dosing is further exacerbated by the fact that the '499 Patent claims a broad range of naltrexone doses (310-480 mg) and, as Alkermes acknowledged, AUC is dose dependent. (Exs. 1027, at 7; 1030 ¶¶ 42, 44, 60.)

Under BRI, however, Alkermes' failure to provide a meaningful definition invites a POSA to use any available data set. Accordingly, the BRI of the above

term allows the use of any data for the AUC of the claimed naltrexone dose compared to any data for the AUC of a 50 mg/day oral dose. (Ex. 1030 ¶ 43.)

C. “about three”

Claim 1 requires “about three.” The term is not specifically defined in the ’499 Patent.

35 U.S.C. § 112, fourth paragraph, requires that a dependent claim further narrow the scope of the claim from which it depends. Here, claim 5 specifies an AUC of about 3.3 times greater than oral dosing. Thus, “about three” necessarily encompasses at least 3.3. This is further supported by the Ehrich Declaration that points to data indicating an AUC of 3.3 times greater than oral dosing as supporting the patentability of both claims 1 and 5.

A POSA would thus appreciate that “about three” also encompasses at least “about 2.7.” (Ex. 1030 ¶¶ 45-47.) But as explained by Dr. Park, this term could encompass a wider range. (*Id.* ¶ 47.)

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.” (Ex. 1001, 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 BRI encompasses no prior oral naltrexone administration, *ever*. (Ex. 1030 ¶ 48.)

E. “initial oral dose”

Claim 11 requires the individual not receive an “initial oral dose” of naltrexone. The ’499 Patent does not define this term. The only reference to dosing in the ’499 Patent is to the administration of naltrexone to treat a patient to overcome his or her addiction. The art, however, makes clear that there are other purposes. For example, Comer teaches the use of naltrexone as part of a detoxification process prior to treatment. (Ex. 1010, 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. (Exs. 1015, 5:65-6:6, 6:13-17; 1011, at 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. (Ex. 1030 ¶ 49.)

F. “about 35% by weight”

Claim 13 requires the long acting formulation be present at a concentration of about 35% by weight. The specification does not specifically define what is meant by “formulation,” but does describe how to produce the microparticles, *i.e.*, 30-75% drug loading. (Ex. 1001, 6:52-54.) A POSA would appreciate that this term refers to the percent by weight of the particle. (Ex. 1030 ¶ 50.)

IX. CLAIMS 1, 3-5, AND 10-12 ARE ANTICIPATED

A. Legal Background

Under 35 U.S.C. § 102(b), “[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.” *Verdegaal Bros. v. Union Oil Co. of Cal.*, 814 F.2d 628, 631, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987). Inherent anticipation requires that the inherent disclosure (1) necessarily results from the material described in the reference, and (2) that it would be eventually recognized by a POSA. *Schering Corp. v. Geneva Pharms.*, 339 F.3d 1373, 1377-78 (Fed. Cir. 2003). Stated otherwise, “[u]nder principles of inherency, if the prior art necessarily functions in accordance with, or includes, the claim limitations, it anticipates.” *Atlas Powder Co. v. IRECO Inc.*, 190 F.3d 1342, 1347 (Fed. Cir. 1999).

**B. Ground 1: Comer Teaches Every
Element Of Claims 1, 3-5, And 10-12**

Claims 1, 3-5, and 10-12 are anticipated by Comer (Ex. 1010)², as interpreted by Nuwayser (Ex. 1014).³ Comer describes testing in human opioid-dependent patients of a depot injection made from 384 mg of naltrexone (Depotrex[®]). (Ex. 1010, at 351-354.) “The active formulation contained drug equivalent to 192 mg naltrexone base...and for the high dose, participants received two naltrexone injections (384 [sic] mg naltrexone base).” (*Id.* at 354; Ex. 1030 ¶ 87.)

While not stated in Comer, *per se*, a POSA would understand from, for example, Nuwayser, that Depotrex[®] is an extended release microcapsule comprising naltrexone and PLGA. 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.” When administered subcutaneously, Depotrex delivered therapeutic levels in six heroin addicts for 30

² Comer was of record but was not applied. A copy of Comer bearing a library date stamp of February 18, 2002, and declaration of the British Library Board are provided. Comer is 35 U.S.C. § 102(b) prior art.

³ Nuwayser was filed on May 31, 2002, with a nonpublication request. Nuwayser is prior art under 35 U.S.C. § 102(e). Nuwayser was not of record.

days. (Ex. 1014, 14:26-50, 19:4-25, Fig. 7.) In addition, a POSA would note the superimposable nature of the AUC plots provided in Figure 1 of Comer and Figure 7 of Nuwayser, which would only serve to underscore the identity of Depotrex referenced in Comer. (Exs. 1010, at 354, Fig. 1; 1014, 19:4-25, Fig. 7; 1030 ¶ 77, 90.) Accordingly a POSA would know that “Depotrex” as referenced in Comer refers to PLGA/naltrexone microcapsules used for depot injection as described in Nuwayser.

Anticipation can be established using a combination of references where—as here—the secondary reference is used merely to establish the meaning of a term to a POSA. *In re Baxter Travenol Labs.*, 952 F.2d 388, 390-91 (Fed. Cir. 1991); *see also* MPEP § 2131.01 [I], [II].

Comer’s depot formulation was injected into the buttocks of the patients using an 18 gauge needle—*i.e.*, parenteral administration. (Ex. 1010, at 354.) Comer determined that this 384 mg dose of depot naltrexone antagonized heroin-induced subjective ratings for five weeks and plasma levels remained above the therapeutic level of 1 ng/ml for approximately four weeks. (*Id.* at 351.) “These results suggest that this depot formulation of naltrexone provides a safe, effective, long-lasting antagonism of the effects of heroin.” (*Id.*; Ex. 1030 ¶ 88.)

Thus, Comer teaches the method of claim 1—treating patients in need of naltrexone (heroin dependent patients) by parenterally administering (depot

injection into the buttocks) a long-acting (1 ng/ml blood levels for four weeks) formulation of about 310 mg to about 480 mg (384 mg) and PLGA (evidenced by Nuwayser). (Ex. 1030 ¶ 89.) The only remaining element of the claim is the observed AUC when compared to a 50 mg/day oral dose.

As discussed by Dr. Park, the plot of Figure 1 of Comer discloses an AUC that is about three times greater than that achieved by 50 mg/day oral administration to the same extent as the '499 Patent. (*Id.* ¶¶ 67-74, 81, 89.) This differential results from comparing the AUC of Comer to the oral data presented in Tice or the Ehrich Declaration, the same oral data used by Alkermes when making its comparison. (*Id.*) So Comer's AUC differential over 50 mg/day oral dosing is about 3, indeed about 3.3.

Moreover, during an appeal filed in the '499 Patent's grandchild, Application No. 13/871,534, filed April 26, 2013 (now abandoned), Alkermes admitted that "[t]he Examiner appears to ignore the fact that the result (superior efficacy and pharmacokinetic profile) is dose dependent..." (Ex. 1027, 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 Alkermes' relied for their observation of alleged unexpected result. (Ex. 1001, 1: 30-40, 8:32-4, 17:49-62.) Since the doses are the same and Alkermes

has admitted that AUC is dose dependent, Comer must also have the claimed AUC differential if compared to the same oral dosing data. (Ex. 1030 ¶¶ 81, 89.)

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

Claim 10 specifies that the patient is alcohol dependent. 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. (Ex. 1010, at 352.) So to a POSA, Comer's result also places the art in possession of treating an alcoholic with a 384 mg depot injection as claimed. Claim 10 is therefore anticipated by Comer. (Ex. 1030 ¶ 92.)

Claim 11 requires that the patient not receive an "initial" dose of naltrexone orally. In Comer, patients did get oral naltrexone, but they did not get the depot injection until two days later. (Ex. 1010, at 353.) That oral dosing in Comer was not an "initial" treatment dose, as it was given for other purposes. Therefore, claim 11 is anticipated. (*See also* Ex. 1010, at 359 ("In a treatment setting where oral naltrexone may not be given prior to depot naltrexone...").) (Ex. 1030 ¶ 93.)

Finally, claim 12 requires that the parenteral administration be an injection. As noted in connection with claim 1, Comer teaches injection into the buttocks, so claim 12 is anticipated. (Exs. 1010, at 354; 1030 ¶ 94.)

C. Ground 2: Nuwayser Teaches Every Element Of Claims 1, 3-5, 11, And 12

Challenged claims 1, 3-5, 11, and 12 are anticipated by Nuwayser (Ex. 1014). In Example IV, Nuwayser describes a formulation of PLGA (65% LA: 35% GA) and 54.4% naltrexone, described as Depotrex, which, when administered subcutaneously, delivered therapeutic levels in six heroin addicts for 30 days. (Exs. 1014, 14:26-50, 19:4-25; 1030 ¶¶ 95-97.) 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 two things to a POSA: (1) that plasma levels of 1 ng/ml could be obtained for at least 28 days; and (2) 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. (Exs. 1014, 19:4-25, Fig. 7; 1030 ¶¶ 75-77, 96.) 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 (Ex. 1027, 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. (Ex. 1030 ¶¶ 75-77, 96.) Since the doses must be the same, the AUC and differential (based on the oral data used by Alkermes) must be the same. Nuwayser anticipates claim 1 of the '499 Patent.

Nuwayser's 28-day release anticipates claim 3, requiring at least two weeks of naltrexone release, and claim 4, and requiring release for four weeks. (Ex. 1030 ¶ 98.) Claim 5 is anticipated for reasons discussed in Ground 1 and claim 1 hereof. 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. (*Id.* ¶¶ 75-77, 81, 89, 98.) Comer resulted in a differential of about 3, indeed, about 3.3. (*Id.*)

Claim 11 requires that the patient not receive an "initial" dose of naltrexone orally. Nothing in Nuwayser discloses giving any prior dose of naltrexone. (*Id.* ¶ 99.) Finally, claim 12 requires that the parenteral administration be an injection. Nuwayser teaches subcutaneous injection ("SC") and therefore anticipates claim 12. (*Id.*)

X. THE CHALLENGED CLAIMS ARE OBVIOUS

A. Legal Background

A patent may not be obtained “if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.” 35 U.S.C. § 103(a). Underlying factual determinations in an obviousness analysis include (1) the scope and content of the prior art, (2) the level of ordinary skill in the art, (3) the differences between the claimed invention and the prior art, and (4) objective indicia of nonobviousness. *See KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007).

“[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.” *In re Aller*, 220 F.2d 454, 456 (C.C.P.A. 1955).

A “[m]otivation to combine may be found in many different places and forms.” *Par Pharm., Inc. v. TWi Pharms., Inc.*, 773 F.3d 1186, 1197 (Fed. Cir. 2014). Thus, for example, a challenger is not limited to the same motivation that the patentee had. *See id.* (citing *Alcon Research, Ltd. v. Apotex Inc.*, 687 F.3d 1362, 1369 (Fed. Cir. 2012)). “When a patent ‘simply arranges old elements with each performing the same function it had been known to perform’ and yields no

more than one would expect from such arrangement, the combination is obvious.”
KSR, 550 U.S. at 417 (quoting *Sakraida v. Ag Pro*, 425 U.S. 273, 282 (1976)).

Where the claimed ranges overlap or lie inside ranges disclosed by the prior art a *prima facie* case of obviousness exists. *In re Wertheim*, 541 F.2d 257 (C.C.P.A. 1976); *see also In re Geisler*, 116 F.3d 1465, 1469-71 (Fed. Cir. 1997). Similarly, a *prima facie* case of obviousness exists where the claimed ranges or amounts do not overlap with the prior art but are merely close. *See Titanium Metals Corp. of Am. v. Banner*, 778 F.2d 775, 783 (Fed. Cir. 1985).

**B. Ground 3: The Challenged Claims Are Obvious
Over Comer In View Of Nuwayser, Rubio⁴, And Wright⁵**

The challenged claims are obvious over Comer in view of Nuwayser as those references are described in Grounds 1 and 2. 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

⁴ A copy of Rubio (Ex. 1028) bearing a library date stamp of September 28, 2001, is provided. Rubio was not of record or considered by the Examiner during prosecution. Rubio is 35 U.S.C. § 102(b) prior art.

⁵ Wright (Ex. 1018) published on July 24, 2001. It is prior art under 35 U.S.C. § 102(e). Wright was of record, but not discussed during prosecution.

(384 mg) and a biocompatible PLGA polymer (Depotrex). (Ex. 1030 ¶¶ 87-89, 100-102.)

If one did not accept that Nuwayser defined Depotrex to a POSA as explained in Ground 1, a POSA would nonetheless be motivated to use the Nuwayser naltrexone formulation in the method taught by Comer with a reasonable expectation of success. Assuming Comer does not specifically describe the specific naltrexone formulation that should be used, a POSA would seek out acceptable formulations. (*Id.* ¶ 102.) Comer teaches a method of treating heroin addicts by using 384 mg naltrexone in parentally injectable naltrexone-containing microcapsules. (Ex. 1010, at 351, 354, 358-359, Fig. 1.) But arguably, except for the dose, Nuwayser teaches the same thing. (Exs. 1014, 19:4-25; 1030 ¶¶ 87-90, 101-102.) And both provide data on the release profile of their formulations, which a POSA would recognize to be the same, or nearly so. (Exs. 1010 Fig. 1; 1014 Fig. 7; 1030 ¶¶ 75-77, 102.)

A POSA would therefore reasonably expect that using sufficient PLGA microparticles produced in accordance with Nuwayser to provide 384 mg dose of naltrexone called for in Comer would achieve the results of Comer, *i.e.*, a 28-day release of a therapeutic dose of naltrexone having a similar release profile and AUC. (Ex. 1030 ¶ 102.) 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. (*Id.* ¶ 103.) Indeed, as Dr. Park noted, when the AUCs of Comer and Nuwayser are compared to the oral data in Tice and in the Ehrich Declaration, the AUC differential is about three, indeed about 3.3 (*Id.* ¶¶ 81, 89, 102-103, 107.)

Given the sameness of the AUC plots of Comer and Nuwayser (*Id.* ¶¶ 75-77), and that both stated that they provided therapeutic doses for about a month, a POSA would also have a reasonable expectation that their combined teachings would be successful. (Exs. 1010, at 351, 359 (“These results suggest that this depot formulation of naltrexone provides a safe, effective long-lasting antagonism of the effects of heroin.”); 1014, 19:23-25 (“This formulation delivered a therapeutic level of naltrexone in six heroin addicts for a period of 30 days (*see* FIG. 7).”); 1030 ¶¶ 101-102, 106-107.)

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. (Ex. 1030 ¶¶ 16, 63-65, 81-86, 106-107.) First, as Dr. Park explains, a POSA would realize that the AUC and AUC differential between a depot injection and oral dosing of naltrexone would not be expected to have a meaningful impact on efficacy. (*Id.* ¶¶ 16, 60-62, 64.) So long as therapeutic blood levels were maintained, which was known in the art to result from oral dosing and

depot injections, the treatment should be equally effective no matter how much higher the blood concentration, *i.e.*, the AUC (assuming compliant use). (*Id.* ¶¶ 44, 52, 54, 60.) Indeed, as Dr. Park explains, it is even possible that an enhanced AUC above levels necessary to minimally maintain therapeutic blood levels could raise toxicity issues. (*Id.* ¶ 60.)

Nothing in the specification would suggest to a POSA that using a naltrexone depot injection (whether it is that described by the '499 Patent, in Comer, or Nuwayser) would provide meaningfully different therapeutic effects than oral dosing 50 mg/day. (*Id.* ¶¶ 16, 61-62.) A depot injection might provide better compliance, but that was known. (Exs. 1010, 351-352; 1030 ¶ 54.) Indeed, when distinguishing oral dosing and other depot injections during prosecution, Alkermes noted that Tice (Ex. 1015) resulted in an AUC that was roughly the same as oral dosing—not three times that level as claimed. (Ex. 1003, at 4.) Alkermes did not argue, however, that either was less effective. (Ex. 1030 ¶¶ 16, 61-62.)

Moreover, a POSA would discount any AUC differential because it did not result from a comparison made to the closest prior art. Here the closest prior art is not oral dosing or Tice, as the Examiner suggested. (*Id.* ¶¶ 24, 63-65.) Instead, a POSA would look to Comer and Nuwayser, alone or in combination, both of which involved administering about 380 mg naltrexone in a PGLA-containing formulation as once-a-month depot injections. (*Id.* ¶¶ 101-107.) Since the dose,

formulation, and manner of administration were exactly the same as that claimed, and the pharmacokinetic plots of each can be superimposed, a POSA would understand that the AUC and differential should all be the same or not patentably different. (*Id.* ¶¶ 64-77, 81, 89, 96, 102-103.)

A POSA would be concerned that the AUC comparisons made in the '499 Patent are hypothetical. Unlike direct comparisons to one-month depot injections, this comparison is based on the use of oral AUC data obtained for a single day. To make a comparison, one must artificially divide or average the one-month data or assume that the one-day's data is consistent and multiply it by 28 days. (*Id.* ¶ 65.) Accordingly, a POSA would not consider any difference in AUC differential to be significant for all the reasons discussed herein, especially considering the sensitivity of the oral data used. (*Id.* ¶¶ 81-86.)

Turning to the dependent claims, claim 2 requires that treatment occur every 4 weeks and last for at least 24 weeks and that there be no prior oral dose of naltrexone. As to the former, treating patients every 4 weeks for 24 weeks or more is obvious. Comer teaches that naltrexone had already been used for "chronic administration of over 1 year." (Ex. 1010, at 351.) Moreover, Rubio teaches that treatment protocols of 12 months in alcoholics were known. (Ex. 1028, at 419-420.) As to the latter limitation, Comer contemplated treating with the depot injection without a prior oral dose of naltrexone. (Ex. 1010, at 359 ("In a treatment

setting where oral naltrexone may not be given prior to depot naltrexone”).) Similarly, Nuwayser has no disclosure of providing its patients with oral doses of naltrexone. Claim 2 is therefore obvious. (Ex. 1030 ¶ 108.)

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

Claim 5 requires that the AUC be about 3.3 times that of 50 mg/day oral dosing. Comer and Nuwayser both disclose this. (*Id.* ¶¶ 81, 89, 109.) Moreover, as just discussed any difference in AUC differential would not carry patentable weight, as the difference is not meaningful in terms of therapeutic efficacy, the differential was not determined by a comparison to the closest art, and the differential is subject to mathematical manipulation.

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

Claims 7-9 require a second dose be given seven days or more after the first one is given, and that the subsequent dose be substantially similar to (claim 8) or the same as (claim 9) to the first dose. As Dr. Park explains, this protocol would be obvious to a POSA. Since Comer and Nuwayser both teach four-week dosing, a

POSA would not consider a second dose earlier than seven days. (*Id.* ¶ 111.) Moreover, if a single 7, 14, or even 30-day period were all that was needed for alcohol or opioid treatment, the very compliance problem that drives the reasoning for a depot injection would not be as compelling. A POSA would expect that more than one four-week dose would be needed. And there is no reason to use different formulations than the one already established as successful. (*Id.*)

Claim 10 specifies that the patient is alcohol dependent. Comer acknowledged that naltrexone had already been established to be safe and effective in alcoholics. (Ex. 1010, at 352.) Rubio teaches treating alcoholics as well. (Exs. 1028, at 419-420; 1030 ¶ 112.)

Claim 11 requires that the patient not receive an “initial” dose of naltrexone orally. As discussed in Grounds 1 and 2, the oral dosing in Comer was not an “initial” dose, and there is no oral dosing suggested in Nuwayser. (Ex. 1030 ¶ 113.) Claim 11 is therefore obvious.

Claim 12 requires that the parenteral administration be an injection. Comer teaches injection into the buttocks. (Ex. 1010, at 354.) Nuwayser teaches subcutaneous (“SC”) injection. (Ex. 1014 Fig. 7.) Claim 12 is therefore obvious. (Ex. 1030 ¶ 113.)

Claim 13 requires that the naltrexone be present in the amount of about 35% by weight of the formulation. Nuwayser exemplifies a formulation that includes

naltrexone in the amount of 54.4% by weight. (Ex. 1014, 19:22-23.) It was well-known that drug loading could be in the range of 30-75% by weight of the formulation. (Exs. 1018, 7:63-8:1; 1030 ¶ 114.)

**C. Ground 4: The Challenged Claims Are Obvious
 Over Nuwayser In View Of Comer, Rubio, And Wright**

Ground 3 was predicated on Comer not teaching the formulation of Depotrex and seeking a formulation to use in its protocol to deliver 384 mg of naltrexone over about a month. Nuwayser provides that teaching, and there is motive for making that combination and a reasonable expectation of success for doing so as explained in Ground 3. Ground 4 is identical, but switches the primary and secondary references, which only really impacts the motivation. (Ex. 1030 ¶ 104.)

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. (Exs. 1014, 14:26-49, 19:4-25, Fig. 7; 1030 ¶ 104.) Nuwayser provides a plot of the pharmacokinetics, including the AUC resulting from the use of these microcapsules. (Ex. 1030 ¶¶ 75-77, 104-106.) The only thing that Nuwayser arguably does not explicitly disclose is 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. (*Id.* ¶¶ 102, 104.)

However, like Nuwayser, Comer describes giving long-acting PLGA 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* Ex. 1010 Fig. 1 *with* Ex. 1014 Fig. 7; Ex. 1030 ¶ 105.) All of this would motivate a POSA looking for an appropriate dose to use that disclosed in Comer, namely 384 mg (about 380 mg). (Ex. 1030 ¶ 106.)

And a POSA would have 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. (*Id.* ¶¶ 106-107.) 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. (*Id.* ¶¶ 75-77, 106-107.) 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). (*Id.* ¶¶ 75-77, 81-89, 103, 106-107.)

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. (*Id.*) Using the inventor's data and/or that of Tice, the AUC differential would be about three, indeed about 3.3. (*Id.*)

To the extent that the dose did not provide the AUC of Nuwayser's Figure 7, as the claimed AUC differential, a POSA could adjust the dose to arrive at that disclosed AUC endpoint of Figure 7. (*Id.* ¶¶ 106, 107.) A POSA could do so assuming that a POSA considered the AUC differential to be significant, which, as discussed in connection with claim 1 of Ground 3, a POSA would not. (*Id.* ¶¶ 60-66, 82-86, 103, 106-107.)

Because the art used in this Ground is identical to that used in Ground 3 except that the order of primary and secondary references is switched, the dependent claims are obvious for the same reasons generally described in Grounds 3. 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. (Exs. 1010, at 352; 1028, at 419, 420; 1030 ¶ 108.) Both Nuwayser and Comer teach one-month dosing and render obvious claims 3 and 4. 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 (Ex. 1030 ¶¶ 75-77, 81, 89, 109). Claim 6 is obvious for the reasons discussed in connection

with claim 2. (*Id.* ¶ 110.) Claims 7-9 are obvious because both Nuwayser and Comer teach monthly dosing and a POSA would use as many of these same dosage forms as needed throughout the course of treatment. (*Id.* ¶ 111.) Claim 10 is obvious as Comer teaches that naltrexone for treatment of alcoholism was safe and effective. (*Id.* ¶ 112.) Claim 11 requires the individual not receive an initial oral dose, and neither Nuwayser nor Comer require such a dose, so claim 11 is obvious. (*Id.* ¶ 113.) Claim 12 is obvious as both references teach injection. (*Id.*) In regards to claim 13, Nuwayser exemplifies a formulation that includes naltrexone in the amount of 54.4% by weight. (Ex. 1014, 19:22-23.) It was well known that drug loading could be in the range of 30-75% by weight of the formulation. (Exs. 1018, 7:65-8:1; 1030 ¶ 114.)

**D. Ground 5: The Challenged Claims Are Obvious
Over Nuwayser In View Of Kranzler, Rubio, And Wright**

The challenged claims are obvious over Nuwayser, as discussed in Grounds 2 and 4, in view of Kranzler⁶ (Ex. 1011), and further in view of Rubio and Wright. Nuwayser describes formulations of extended release microcapsules of naltrexone (65:35 PLGA and 54.4% naltrexone by weight) and explains that the

⁶ A copy of Kranzler bearing a library date stamp September 18, 1998 and declaration of the British Library Board are provided. Kranzler was not considered by the Examiner during prosecution. Kranzler is 35 U.S.C. § 102(b) prior art.

microcapsules can be subcutaneously implanted in heroin dependent patients to provide therapeutic levels of naltrexone for a period of 30 days. (Exs. 1014, 14:26-49, 19:4-25, Fig. 7; 1030 ¶ 115.) Nuwayser provides a plot of the pharmacokinetic properties resulting from the use of these microcapsules. (Exs. 1014, 14:26-49, 19:4-25, Fig. 7; 1030 ¶¶ 75-77, 115.) It would be obvious to determine the dose that resulted in the disclosed AUC without undue experimentation by generating a standard curve. (Ex. 1030 ¶ 116.)

It would require nothing more than routine experimentation to prepare an AUC-dose standard curve to find a dose for any given AUC, and thus arrive at the AUC endpoint disclosed in Nuwayser's Figure 7. (*Id.*) While nothing more should be needed, Kranzler already established that 206 mg naltrexone delivered by a depot injection provided three weeks of 1 ng/ml blood levels. (Ex. 1011, at 1074 Abstract.) This would provide at least a starting point for a POSA, if necessary, and would suggest to a POSA that additional naltrexone would be needed for longer duration of action. It would therefore further motivate a POSA to prepare a standard curve showing the relationship between AUC and the administered dose. (Ex. 1030 ¶ 117.)

As to the resulting AUC being three times that of 50 mg/day oral dosing, the claims are obvious. As noted previously, Nuwayser resulted in an AUC differential of about three, indeed about 3.3, when compared to the oral data of the Tice and

Ehrich Declarations. (*Id.* ¶¶ 75-77, 81, 89, 106, 107, 118.) Moreover, the dose of Nuwayser that resulted in the described AUC curve should fall within the claim range. (*Id.*) It should, in fact, be about 380 mg, as AUC is dose-dependent and the AUC of Nuwayser is the same as that of Comer, both resulting from parenteral administration of 384 mg naltrexone. (*Id.*) The AUC differential should be the same as well.

As noted previously, the dose should be adjustable as needed and should render the claimed AUC differential obvious. That again assumes a POSA would feel compelled to adjust the dose to match the plot of Fig. 7. But for the reasons described previously, including the failure to compare with the closest prior art, the lack of meaningful link to efficacy, and the subjectivity of the data to manipulation, this limitation is entitled to little patentable weight, and a POSA might consider any adjustment unnecessary. (*Id.* ¶¶ 103, 118.) Thus, a POSA would consider any difference in AUC and AUC differential to be inconsequential.

Turning to the dependent claims, claim 2 requires that treatment occur every 4 weeks and last for at least 24 weeks, and that there be no prior oral dose of naltrexone. As to the former, treating patients every four weeks for 24 weeks or more is obvious. Rubio teaches treatment regimens of 12 months in alcoholics. (Ex. 1028, at 419-420.) Nuwayser has no disclosure requiring oral doses of naltrexone. (Ex. 1030 ¶ 119.) Claim 2 is therefore obvious. Claims 3 and 4 are

obvious for the reasons discussed in Ground 2, as Nuwayser teaches 30-day release. (*Id.* ¶ 120.)

Claim 5 is obvious for the reasons discussed in Grounds 2 and 4 and claim 1 above, namely, that Nuwayser discloses or renders obvious a dose of about 380 mg and provides an AUC differential of about 3.3. (*Id.* ¶¶ 75-77, 81, 89, 120.) Claim 6 requires that the treatment last at least 24 weeks. This claim is obvious for the reasons described in connection with claim 2, which includes the same limitation. (*Id.* ¶ 121.)

Claims 7-9 require a second dose be given 7 days or more after the first dose, and that the subsequent dose be substantially similar to (claim 8), or the same as (claim 9), the first dose. As Dr. Park explains, this would be obvious to a POSA. Since Nuwayser teaches once-a-month dosing, a POSA would not consider a second dose earlier than seven days. Moreover, if a single seven, fourteen, or even thirty-day period were all that was needed for alcohol or opioid treatment, the compliance problem that drives the very reasoning behind the use of a depot injection would not be as compelling. A POSA would expect that more than one dose would be needed. (*Id.* ¶ 121.) Having developed a first depot formulation that is safe and effective, it is obvious that the same formulation would be used again. Claims 7-9 are therefore obvious.

Claim 10 specifies that the patient is alcohol dependent. The patients in the Nuwayser study were opioid dependent. However, Kranzler teaches that high dose depot injections of naltrexone were safe and effective in treating alcohol addiction. (Ex. 1011, at 1074, 1077-78.) Claim 10 is therefore obvious. (Ex. 1030 ¶ 122.)

Claim 11 requires that the patient not receive an “initial” dose of oral naltrexone. As noted in the context of claim 2, Nuwayser says nothing about an earlier dose of oral naltrexone. Moreover, although Kranzler discloses oral naltrexone as part of the detoxification protocol, there is a two-week drug-free interval before the depot is given. (Ex. 1011, at 1074-75.) These earlier doses are not “initial” oral doses as claimed. Claim 11 is therefore obvious. (Ex. 1030 ¶ 123.)

Claim 12 requires that the parenteral administration be an injection. As noted in connection with claim 1, Nuwayser teaches “SC” or subcutaneous injection (Ex. 1014 Fig. 7), and Kranzler teaches injection of either naltrexone or placebo depots. (Ex. 1011, at 1074.) Claim 12 is therefore obvious. (Ex. 1030 ¶ 124.)

Claim 13 requires that the naltrexone be present in a concentration of about 35% by weight of the formulation. Nuwayser exemplifies a formulation that includes naltrexone in the amount of 54.4% by weight. (Ex. 1014, 19:22-23.) It was also well-known that drug loading could be in the range of 30-75% by weight of the formulation. (Exs. 1018, 7:65-8:1; 1030 ¶ 125.)

E. Ground 6: The Challenged Claims Are Obvious Over Alkermes' 10-K In View Of The Vivitrex Specimen, Rubio, And Wright

The challenged claims are unpatentable over Alkermes' July 1, 2002 Form 10-K ("Alkermes' 10-K," Ex. 1016),⁷ in view of the specimen Alkermes submitted to the USPTO to support its trademark application for the mark VIVITREX ("Vivitrex Specimen") (Ex. 1017),⁸ further in view of Alkermes' U.S. Patent No. 6,264,987 to Wright *et al.* ("Wright") (Ex. 1018).

⁷ Alkermes' 10-K (Ex. 1016) was not of record during prosecution. The Alkermes' 10-K was electronically filed on the Securities and Exchange Commission's ("SEC") EDGAR System on July 1, 2002. (Ex. 1058.) According to the SEC, companies were required to file 10-K documents electronically at that time. (Ex. 1059.) This document would have been immediately uploaded and available. (Ex. 1060.) Accordingly, the 10-K was available for public viewing on or about July 1, 2002. Alkermes' 10-K was not considered by the Examiner during prosecution. Alkermes' 10-K is prior art under 35 U.S.C. § 102(b).

⁸ The Vivitrex Specimen was not of record during prosecution. The Vivitrex Specimen was provided to the USPTO as evidence of use in commerce "at least as early as August 7, 2002." (Ex. 1017.) The Vivitrex Specimen was not considered by the Examiner during prosecution. It is prior art under 35 U.S.C. § 102(b). The Vivitrex trademark was allowed on December 10, 2002, and published in the

Alkermes' 10-K discloses "we are developing VivitrexTM, a Medisorb formulation of naltrexone, for the treatment of alcoholism and opiate dependence." (Ex. 1016, at 3.) Alkermes' 10-K states that Vivitrex is a "Medisorb" formulation, which is an "injectable extended-release technology and is designed to provide once-a-month dosing to enhance patient adherence by removing the need for daily dosing." (*Id.* at 5; Ex. 1030 ¶¶ 126-128.)

By its use of "TM," Alkermes' 10-K indicates to the public that Alkermes considered "Vivitrex" to be a trademark. This would lead a POSA to check whether or not there was a pending trademark registration at the time of the 10-K filing. That, and the public availability of trademark records, would lead an

Official Gazette, Vol. 1265, No. 2, on the same day. A library date stamp copy dated January 8, 2003 of the *Official Gazette* is provided (Ex. 1020). According to the third edition of the *Trademark Manual of Examining Procedure (TMEP)* dated January 2002 (Ex. 1041), the Trademark Applications and Registrations Retrieval (TARR) database provided "up to the minute information" regarding the status and prosecution history of trademark applications and registrations. This information was available 24 hours a day, seven days a week. (*Id.* 100-5.) Accordingly, the Vivitrex Specimen was publically available, at least as early as December 10, 2002.

interested POSA to USPTO records. The POSA would find an application and Vivitrex Specimen deposited with the United States Postal Service on August 15, 2002, and submitted to the USPTO, to support Alkermes' trademark filing. According to Alkermes' "Allegation of Use of Mark under 15 U.S.C. § 1051(c) or (d)," the Vivitrex mark was being used in commerce "at least as early as August 7, 2002." (Ex. 1017, at 4.) Alkermes stated that the mark was being used "in connection with Polymer-based Drug Delivery Formulations for Clinical Use and Pharmaceutical Products, namely, Injectable Drug Delivery Formulations." The accompanying Vivitrex Specimen states, "CONTENTS: Medisorb[®] Naltrexone (190 mg or 380 mg) for injectable suspension." (*Id.* 5; Ex. 1030 ¶ 130.) The mark was allowed on December 10, 2002. (Ex. 1020.)

Neither the 10-K nor the Vivitrex Specimen goes into detail on Medisorb formulations, but Alkermes' own Wright (Ex. 1018) explains the Medisorb technology and how it can be used to produce, *inter alia*, naltrexone microparticles from PLGA having varying proportions of LA and GA, *i.e.*, 75:25, 85:15, 65:35.) (*Id.* 7:48-8:60; Ex. 1030 ¶ 131.) Wright states that the molecular weight of the polymer affects drug release characteristics and influences the biodegradation rate of the polymer. (Exs. 1018, 1:33-38; 1030 ¶ 132.) It is not said to significantly influence AUC. Just for purposes of confirmation, the '499 Patent acknowledges that Wright discloses that the Medisorb technology can be used in its

microparticles and, indeed, as Dr. Park explains, the method of making the particles of the '499 Patent is virtually identical to that described in Example 3 of Wright (Exs. 1001, 3:3-33, 5:35-8:2; 1018, 7:50-8:60; 1030 ¶¶ 132-133.) In essence, the 10-K provides the method, the Specimen clarifies that Vivitrex is either 190 or 380 mg, and Wright explains how to make the Vivitrex formulation.

The only remaining element of the claim not expressly found in these disclosures is the recited difference in serum AUC of naltrexone when compared to a 50 mg/day oral dose. (Ex. 1030 ¶ 134.) Based on Wright, a POSA could make three different types of PLGA naltrexone microparticles (Ex. 1018, 1:33-38.) These three types are the same naltrexone microparticles described in the '499 Patent. It would be readily apparent to a POSA that at least one of these three particles was used in the study of the '499 Patent and would result in the same AUC as identified in the '499 Patent. But, more importantly, all three have the same dose administered the same way from extremely similar formulations. (Ex. 1030 ¶¶ 132-134.)

As discussed previously, AUC is a function of the total amount of drug, not the ratio of polymer. (Ex. 1030 ¶¶ 57, 135.) Therefore, the claimed AUC and AUC differential would result from, or be obvious, using any of Wright's 65:35, 75:25 and 85:15 Medisorb microparticles in the amount disclosed in the Vivitrex Specimen. (Ex. 1030 ¶¶ 134-135.) Indeed, as these are the very same Vivitrex

particles used in the study of the '499 Patent and the Ehrich Declaration, a POSA would expect the AUC and AUC differential from at least one of the three particles made to be the same as that claimed. (*Id.*) Furthermore, as discussed in Grounds 1-5, AUC itself is of questionable patentable weight, and the comparison made in the claim to oral dosing was not a comparison to the closest prior art. Therefore, the AUC claimed should be obvious over the AUCs that resulted from any of these three Medisorb microparticles.

Turning to the dependent claims, claim 2 requires that treatment occur every four weeks and last for at least 24 weeks, and that there be no prior oral dose of naltrexone. Treating patients every 4 weeks for 24 weeks or more is obvious. The 10-K teaches that the clinical trial included repeat doses of Vivitrex. Moreover, treatments lasting more than 24 weeks were known. (Ex. 1028, at 419, 420.) And, as discussed in detail by Dr. Park, it was well-known to administer naltrexone formulations for periods of 24 weeks or more. (Ex. 1030 ¶ 136.) Regarding no prior oral dose of naltrexone, as noted in Section VIII.E, *supra*, the BRI of this latter term is no prior oral administration of naltrexone at all. Nothing in Exhibits 1016-1018 teach the need for prior oral dosing. Claim 2 is therefore obvious.

Claim 3 requires at least two weeks of naltrexone release, and claim 4 requires release for four weeks. The 10-K states that the Vivitrex is administered

monthly. (Ex. 1016, at 3, 5.) Claims 3 and 4 are therefore obvious. (Ex. 1030 ¶ 137.)

Claim 5 requires that the dose be about 380 mg and that the AUC differential be about 3.3 times that of 50 mg/day oral dosing. This limitation was based on the clinical testing noted above in the context of claim 1, which was based on the same Vivitrex particles disclosed in Exhibits 1016-1018. Since the formulations of Vivitrex and those used in the '499 Patent are the same, at least in terms of dose (about 380 mg), and AUC is dose-dependent, the AUCs should be the same, or not unobviously different, no matter which exact ratio of LA and GA from Wright's Examples are used. When compared to the oral data of Tice or the Ehrich Declaration, the differential should be the same as claimed as well. (Ex. 1030 ¶¶ 78-81.) Claim 5 is therefore obvious. (*Id.* ¶ 138.) Claim 6 requires that the treatment last at least 24 weeks. Claim 6 is obvious for the reasons described in connection with claim 2. (*Id.* ¶ 136.)

Claims 7-9 require a second dose be given seven days or more after the first dose, and that the subsequent dose be substantially similar to (claim 8), or the same as (claim 9), the first dose. As Dr. Park explains, this would be obvious to a POSA because a POSA would expect that more than one dose would be needed. (Exs. 1016, at 5-6; 1030 ¶ 139.) Having developed a first depot formulation that is safe and effective, it is obvious that that formulation would be used again.

(Ex. 1030 ¶ 139.) In addition, the 10-K states that the clinical trial tested “repeated doses of Vivitrex administered monthly to alcohol-dependent patients.” (Ex. 1016, at 5-6.) Claims 7-9 are obvious. (Ex. 1030 ¶ 139.) And the described dosage form gave a monthly release, so a POSA would know it should be dosed again seven days or more after the first dose.

Claim 10 specifies that the patient is alcohol dependent. The 10-K states that Vivitrex is used “for the treatment of alcohol.” (Exs. 1016, at 3; 1030 ¶ 140.) Claim 10 is therefore obvious.

Claim 11 requires that the patient not receive an “initial” dose of naltrexone orally. As noted in the context of claim 2, none of the relied upon references in this ground teaches or suggests using an initial dose. (Ex. 1030 ¶ 141.) Claim 11 is therefore obvious.

Claim 12 requires that the parenteral administration be an injection. As noted in connection with claim 1, the 10-K teaches “injectable extended-release technology” and the Specimen states “injectable drug delivery formulations” (Exs. 1016, at 3; 1017, at 3, 5; 1030 ¶ 142.) Claim 12 is therefore obvious.

Claim 13 requires that the naltrexone be present in the amount of about 35% by weight of the formulation. Wright teaches drug loadings of 30-75%, thus rendering claim 13 obvious. (Exs. 1018, 7:65-8:1; 1030 ¶ 143.)

XI. CLAIMS CHART

Claim	Citation
1(a). A method for treating an individual in need of naltrexone comprising the step of	<u>Ground 1:</u> Ex. 1010, at 351 (“These results suggest that this depot formulation of naltrexone provides a safe, effective, long-lasting antagonism of the effects of heroin.”), at 352 (“participants were dependent on heroin”), Fig. 1 <u>Ground 2:</u> Ex. 1014, 19:21-25, Fig. 7 <u>Grounds 3 and 4:</u> See 1(a) of Grounds 1 and 2 <u>Ground 5:</u> See 1(a) of Ground 2 Ex. 1011 Abstract, 1074, 1077 (“bioavailability, tolerability, and efficacy of SRP of NTX for the treatment of alcohol dependence”) <u>Ground 6:</u> Ex. 1016, at 3
1(b). parenterally administering a long acting formulation comprising	<u>Ground 1 :</u> Exs. 1010 Abstract, 354 (“Depot naltrexone (Depotrex[®]), 359 (“long-lasting antagonism”); 1030 ¶ 34 <u>Ground 2:</u>

Claim	Citation
	Exs. 1014, 6:6-9, 14:25-49, 19:4-25, Fig. 7; 1030 ¶ 34 <u>Grounds 3 and 4:</u> See 1(b) of Grounds 1 and 2. <u>Ground 5:</u> See 1(b) of Ground 2 Ex. 1011, at 1074-5, 1077 <u>Ground 6:</u> Exs. 1016, at 5 (“injectable extended-release technology”); 1030 ¶ 34
1(c). about 310 mg to about 480 mg of naltrexone	<u>Ground 1, 3, and 4:</u> Ex. 1010, at 352 (“six received 192 mg depot naltrexone, and six received 384 mg depot naltrexone”), <i>id.</i> 354 <u>Grounds 2 and 5:</u> Exs. 1014, 6:6-9, 14:25-49, 19:4-25, Fig. 7; 1030 ¶¶ 75-77, 95-96, 115-117 <u>Ground 6:</u> Ex. 1017, at 5
1(d). and a biocompatible polymer to the individual	<u>Ground 1:</u> Exs. 1010 Abstract, 352 (“a new depot formulation of naltrexone (Depotrex[®])”), 354 (“Depot naltrexone (Depotrex[®]) was manufactured by Biotek Inc....Depotrex is a registered trademark of Biotek Inc.”); 1014, 6:6-9, 14:25-49, 19:4-25, Fig. 7;

Claim	Citation
	1030 ¶¶ 90, 102-104 <u>Ground 2:</u> Ex. 1014, 6:6-9, 14:25-49, 19:4-25, Fig. 7 <u>Ground 3 and 4:</u> See citations to Exs. 1010, 1014, 1030 in 1(d) of Grounds 1 and 2. <u>Ground 5:</u> See citations to Ex. 1014 in 1(d) of Grounds 1 and 2. See also Exs. 1011, at 1075 <u>Ground 6:</u> Exs. 1016, at 3; 1017, at 5; 1018, 7:50-8:60, 12:33-40; 1030 ¶¶ 131-133
1(e). wherein the serum AUC of naltrexone is about three times greater than that achieved by 50 mg/day oral administration	<u>Ground 1:</u> Exs. 1010 at 354 (“Figure 1 shows mean plasma levels of naltrexone (left panel)”), Fig. 1; 1030 ¶¶ 67-74, 81, 89, 101-103 <u>Ground 2:</u> Exs. 1014, 6:6-9, 14:25-49, 19:4-25, Fig. 7; 1030 ¶¶ 75-77, 81, 89, 95-97, 104-106, 116-117 <u>Grounds 3 and 4:</u> See 1(e) of Grounds 1 and 2 <u>Ground 5:</u>

Claim	Citation
	See 1(e) of Ground 2 <u>Ground 6:</u> Ex. 1030 ¶¶ 78-81, 134-135
1(f). and wherein the biocompatible polymer is a polylactide-co-glycolide polymer.	See 1(d) of Grounds 1-6
2. 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.	<u>Grounds 3-5:</u> Exs. 1010, at 359 (“where oral naltrexone may not be given prior to depot naltrexone”); 1028, at 419-420; 1030 ¶¶ 48, 108, 119 <u>Ground 6:</u> Exs. 1028, at 419-420; 1030 ¶¶ 48, 136
3. The method of claim 1 wherein the long acting formulation releases naltrexone for a period of at least two weeks.	<u>Grounds 1-5:</u> See 1(b) of Grounds 1-5. Ex. 1030 ¶¶ 91 (Gr.1), 98 (Gr.2), 109 (Gr.3-4), 120 (Gr.5) <u>Ground 6:</u> Exs. 1016, at 3 (“once-a-month dosing”); 1030 ¶ 137
4. The method of claim 1 wherein the long acting formulation releases naltrexone for a period of about four weeks.	<u>Grounds 1-5:</u> See 1(b) of Grounds 1-5 above. Ex. 1030 ¶¶ 91 (Gr.1), 98 (Gr.2), 109 (Gr.3-4), 120 (Gr.5) <u>Ground 6:</u>

Claim	Citation
	Exs. 1016, at 3 (“once-a-month dosing”); 1030 ¶ 137
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.	<u>Grounds 1-6:</u> See 1(c) and 1(e) of Grounds 1-6 above. Ex. 1030 ¶¶ 91 (Gr.1), 98 (Gr.2), 109 (Gr.3-4), 120 (Gr.5), 138 (Gr.6)
6. The method of claim 1 wherein the long acting formulation is administered over a period of about 24 week period or longer.	<u>Grounds 3-4</u> Exs. 1010, at 351; 1028, at 419-420; 1030 ¶ 110 <u>Grounds 5-6:</u> Exs. 1028, at 419-420; 1030 ¶¶ 121 (Gr.5), 136 (Gr.6)
7. 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.	<u>Grounds 3-4:</u> Exs. 1010 Abstract; 1014, 19:22-25, Fig. 7; 1030 ¶ 111 <u>Ground 5:</u> Exs. 1014, 19:22-25, Fig. 7; 1030 ¶ 121 <u>Ground 6:</u> Exs. 1016, at 5-6 (“repeated doses of Vivitrex administered monthly to alcohol-dependent patients.”); 1030 ¶ 139
8. The method of claim 7 wherein the second long acting	<u>Grounds 3-4:</u> See claim 7 above

Claim	Citation
formulation is substantially similar to the first long acting formulation.	<u>Ground 5:</u> See claim 7 above <u>Ground 6:</u> See claim 7 above
9. The method of claim 7 wherein the second long acting formulation is the same as the first long acting formulation.	<u>Grounds 3-4:</u> See claim 7 above <u>Ground 5:</u> See claim 7 above <u>Ground 6:</u> See claim 7 above
10. The method of claim 1 wherein the individual is an individual afflicted by alcohol dependency.	<u>Grounds 1, 3-4:</u> Exs. 1010, at 352, (“safe and effective in treating alcohol dependence”); 1028, at 419-420 <u>Ground 5:</u> Exs. 1011 Abstract, at 1077 (“efficacy of SRP of NTX for the treatment of alcohol dependence.”); 1028, at 419-420 <u>Ground 6:</u> Ex. 1016, at 3 (“for the treatment of alcoholism”)
11. The method of claim 1 wherein the individual does not receive an initial oral dose of naltrexone.	<u>Ground 1:</u> Exs. 1010, at 353 (detoxification then two day break before depot); 1030 ¶¶ 49, 93

Claim	Citation
	<u>Ground 2:</u> Exs. 1014, 6:6-9, 14:25-49, 19:4-25, Fig. 7; 1030 ¶ 99 <u>Ground 3-4:</u> See Grounds 1 and 2 of claim 11. <i>See also</i> Exs. 1011, at 1074-75 (2 week medication free period followed by injection); 1030 ¶¶ 49, 113 <u>Ground 5:</u> See Ground 2 of claim 11; Ex. 1030 ¶¶ 49, 123 <u>Ground 6:</u> Ex. 1030 ¶ 141
12. The method of claim 1 wherein naltrexone is administered by injection.	<u>Grounds 1 through 6:</u> See 1(b) for Grounds 1-6 above.
13. The method of claim 1 wherein the naltrexone is present in the long acting formulation at a concentration of about 35% by weight.	<u>Grounds 3-6:</u> Exs. 1018, 7:65-8:1 (“30-75%”); 1030 ¶¶ 50, 114 (Gr.3-4), 125 (Gr.5), 143 (Gr.6)

XII. SECONDARY CONSIDERATIONS

It is Alkermes’ burden to establish secondary indicia of nonobviousness, if any. Alkermes did not offer any evidence during prosecution of the ’499 Patent of commercial success, copying, long-felt but unmet need, skepticism, and industry acclaim. And as discussed previously, Alkermes will likely be unsuccessful in

proving the existence of unexpected and superior results, or that there is a nexus between any secondary indicia, such as commercial success, and the claims of the '499 Patent.

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

Even if, for sake of argument, one accepted that about three times the claimed AUC difference was unexpected, there is nothing on the record to establish that this is a superior result. *In re Soni*, 54 F.3d 746, 750-51 (Fed. Cir. 1995) (“Mere improvement in properties does not always suffice to show unexpected results.”); see also *Steadymed Ltd. v. United Therapeutics Corp.*, IPR2016-00006, Paper 82, Final Written Decision (Mar. 31, 2017), at 65-66.

If a higher AUC value correlated to meaningfully superior efficacy, surely the '499 Patent or the Ehrich Declaration would have said so. Tellingly, neither makes such an argument. In this instance, the AUC “discovery” is a distinction without a difference. *See Galderma Labs., LP v. Tolmar, Inc.*, 737 F.3d 731, 739 (Fed. Cir. 2013) (Unexpected results that are probative of nonobviousness are those that are “different in kind and not merely in degree from the results of the prior art.”). *See In re Harris*, 409 F.3d 1339, 1344 (Fed. Cir. 2005) (affirming obviousness rejection where 32–43% increase in stress rupture life was not a “difference in kind”).

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

Moreover, to prove commercial success, Alkermes must establish that any commercial success it enjoyed was based on patentable features—features of its invention that were not disclosed in the prior art. *See Asyst Techs., Inc. v. Emtrak, Inc.*, 544 F.3d 1310, 1316 (Fed. Cir. 2008); *see also J.T. Eaton & Co. v. Atl. Paste & Glue Co.*, 106 F.3d 1563, 1571 (Fed. Cir. 1997). The commercial success of Alkermes’ Vivitrol product is meaningless unless it can be attributed to the

claimed features of the '499 Patent. Here, all of the claimed features, even the purported AUC differential, were known or obvious. More importantly, Vivitrol is prescribed because it provides an effective treatment, not because it provides a higher AUC than some other treatment.

Finally, as previously recognized by the Federal Circuit, market entry here has been precluded by a complex regulatory scheme. Accordingly, any inference of nonobvious based on commercial success is “weak.” *Merck & Co. v. Teva Pharms.*, 395 F.3d 1364, at 1377 (Fed. Cir. 2005). There are also significant issues as to the commensurateness of any showing. There are currently 16 patents listed in the Orange Book for Vivitrol. (Ex. 1042.) Is the commercial success enjoyed, if any, attributable to the '499 Patent or one of the 15 others? And Alkermes' showing, at best, was for a 380 mg dose. It has not provided sufficient evidence to support the claimed dose range of 310-480 mg despite acknowledging dose-dependence.

XIII. CONCLUSION

For the foregoing reasons, Petitioner requests that *Inter Partes* Review be instituted for claims 1-13 of the '499 Patent, and that those claims be held unpatentable over each of the grounds discussed above.

**XIV. STATEMENT OF PRECISE
RELIEF REQUESTED (37 C.F.R. § 42.22(a))**

Pursuant to 37 C.F.R. §42.22(a), the information presented establishes a reasonable likelihood that Petitioner will prevail with respect to at least one of the claims challenged herein. Accordingly, Petitioner requests institution of an *Inter Partes* Review and cancellation of the challenged claims of the '499 Patent. The text of challenged claims is included in the claim chart in Part XI above.

XV. MANDATORY DISCLOSURES (37 C.F.R. § 42.8(a)(1))

A. Notice Of Each Real Party-In-Interest (37 C.F.R. § 42.8(b)(1))

Petitioner is the real party-in-interest for this proceeding. The '499 Patent is assigned on its face to Alkermes Pharma Ireland Limited.

B. Notice Of Related Matters (37 C.F.R. § 42.8(b)(2))

Petitioner is not aware of any related matters that would affect, or be affected by, a decision in this proceeding.

C. Designation Of Lead And Backup Counsel (37 C.F.R. § 42.8(b)(3))

Pursuant to 37 C.F.R. §§ 42.8(b)(3), 42.8(b)(4), and 42.10(a), Petitioner provides the following designation of Lead and Back-Up counsel:

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

Please address all correspondence to the lead and backup counsel at the address shown above. Petitioner consents to electronic service by e-mail at the above-listed e-mail addresses.

E. Grounds For Standing (37 C.F.R. § 42.104(a))

Petitioner certifies that the '499 Patent is available for IPR and Petitioner is not barred or estopped from requesting IPR of its challenged claims. The fee for this Petition has been paid. The Office is hereby authorized to charge any fee deficiencies, or credit any overpayments, to Deposit Account No. 12-1095 in connection with this petition.

Respectfully submitted,

Dated: April 20, 2018

By: s/ Nichole M. Valeyko /
Nichole M. Valeyko

Case IPR2018-00943 (Patent No. 7,919,499)
Petition for *Inter Partes* Review

Registration No. 55,832

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CERTIFICATE OF COMPLIANCE
WITH TYPE-VOLUME LIMITATION

Pursuant to Rule 37 C.F.R. § 42.24(d), the undersigned hereby certifies that, based upon the word count of the word-processing system used to prepare this petition, the number of words in this petition is 13,617. Pursuant to 37 C.F.R. § 42.24(a), this word count does not include “a table of contents, a table of authorities, a certificate of service or word count, exhibits, appendix, or claim listing.”

Dated: April 20, 2018

By: s/ Nichole M. Valeyko /
Nichole M. Valeyko
Registration No. 55,832

CERTIFICATE OF SERVICE

The undersigned hereby certifies that a copy of the foregoing **PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 7,919,499**, together with all exhibits, Power of Attorney, and all other papers filed therewith, were served on April 20, 2018, as follows.

VIA FEDEX

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