

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AMNEAL PHARMACEUTICALS LLC,
Petitioner

v.

ALKERMES PHARMA IRELAND LIMITED,
Patent Owner

Case IPR2018-00943
Patent 7,919,499

**Patent Owner's Response
to Petition for *Inter Partes* Review
of U.S. Patent No. 7,919,499**

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2004	“Drug Facts: Treatment Approaches for Drug Addiction” published by the National Institute on Drug Abuse (https://www.drugabuse.gov/publications/drugfacts/treatment-approaches-drug-addiction (revised January 2018))	X
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2013	June 2, 2014 Alkermes Comment to Docket No. FDA-2007-D-0369, Draft Guidance for Industry Describing Product-Specific Bioequivalence Recommendations for Naltrexone Extended Release Suspension/Intramuscular (https://www.regulations.gov/document?D=FDA-2007-D-0369-0291)	X

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2016	December 23, 2005 Division Director Approvable Memo for NDA No. 21897(https://www.accessdata.fda.gov/drugsatfda_docs/nda/2006/021897_toc_Vivitrol.cfm)	X
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2021	Annual Report Pursuant to Section 13 or 15(d) of the Securities Exchange Act of 1934 for Alkermes PLC, Form 10-K, for the fiscal year ended December 31, 2017 (http://phx.corporate-ir.net/External.File?item=UGFyZW50SUQ9NjkzNjEzfENoaWxkSUQ9NDA0ODMwfFR5cGU9MQ==&t=1)	X
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2032	Saghir & Schultz, Low-Dose Pharmacokinetics and Oral Bioavailability of Dichloroacetate in Naïve and GSTζ-Depleted Rats, Environmental Health Perspectives, 110(8) 757–763 (Aug. 2002)	
2033	Swanson et al., Development of a New Once-a-Day Formulation of Methylphenidate for the Treatment of Attention-deficit/Hyperactivity Disorder, Arch Gen Psychiatry, 60 204–211 (Feb. 2003)	
2034	Remington: The Science and Practice of Pharmacy, (2000)	
2035	Berkland et al., “Precise control of PLG microsphere size provides enhanced control of drug release rate,” J. Controlled Release 82 137–138 (2002)	
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2037	“FDA Approves Injectable Drugs to Treat Opioid-Dependent Patients,” PR Newswire (Oct. 2010) (https://www.prnewswire.com/news-releases/fda-approves-injectable-drug-to-treat-opioid-dependent-patients-104818409.html)	
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2040	“Medication Assisted Treatment for Opioid Addiction Phased Approach,” Quantum Units Education	
2041	Comer et al., “Injectable, sustained-release naltrexone for the treatment of opioid dependence: a randomized, placebo-controlled trial,” Archives of General Psychiatry, 63(2):210–18 (2006)	
2042	Bardo et al., “Chronic naltrexone increases opiate binding in brain and produced supersensitivity to morphine in the locus coeruleus of the rat,” Brain Res. 19 223–234 (1983)	
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2054	Merriam-Webster’s Collegiate Dictionary, Eleventh Edition (2003) (excerpt)	
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I. Introduction

U.S. Patent No. 7,919,499 (“the ’499 patent”) claims inventions relating to Vivitrol[®],¹ an extended-release injectable formulation of naltrexone developed by Alkermes Pharma Ireland Limited (“Alkermes”). The FDA approved Vivitrol in 2006 for the treatment of alcohol dependence and in 2010 for the prevention of relapse to opioid dependence following opioid detoxification. (Ex. 2001; Ex. 2002; Ex. 2003.)

Vivitrol is a breakthrough in the treatment of alcohol and opioid addiction. It is the first FDA-approved, long-acting injectable formulation of naltrexone (a non-opioid, non-addictive active ingredient), having 380 mg of the drug in a single injection. (Ex. 2020 at 1–2; Ex. 2003.) So significant was the development of this long-acting (“depot”) formulation of naltrexone that the FDA “merited [Vivitrol] priority review,” indicating that Vivitrol is a “significant improvement” over existing treatments. (Ex. 2016 at 1; Ex 2046 at 24.) Since approval, Vivitrol has received significant praise, including in the prestigious New England Journal of Medicine. (Ex. 2043.) It has enjoyed significant commercial success, with 2017 sales of about \$270 million. (Ex. 2021 at 56.)

¹ Vivitrol was previously called Vivitrex. (Ex. 1050 at 742.)

Ignoring the breakthrough that the '499 patented invention represents, Petitioner asserts invalidity based on prior art largely consisting of publications from parties that failed in their own attempts to develop a FDA-approved depot injection of naltrexone. (*e.g.*, Ex. 1010; Ex. 1011; Ex. 1014.)

Specifically, the Petition asserts that claims 1–13 of the '499 patent (“the contested claims”) were either (i) anticipated by Comer (Ex. 1010) or Nuwayser (Ex. 1014), as addressed in Grounds 1 and 2, or (ii) obvious over various combinations of at least one of those references in view of Rubio (Ex. 1028), Wright (Ex. 1018), Kranzler (Ex. 1011), Alkermes’s 10-K (Ex. 1016), and the Vivitrex Specimen (Ex. 1017), as addressed in Grounds 3–6. (Pet. at 4.)

As a threshold matter, the claims should be confirmed because the asserted grounds fail to disclose “the step of parenterally administering a long acting formulation,” which requires a *single* injection of about 310 mg to about 480 mg of naltrexone. The '499 patent’s specification and prosecution history make clear that this is a key claim limitation, and it cannot be ignored. Yet Petitioner’s primary references, Comer and Nuwayser, each require two injections to reach the claimed range of doses. Kranzler, which actually “tested a *single* injection of the same formulation” used by Comer (Ex. 1010 at 359 (emphasis added)²), suggested

² All emphasis in this brief is added unless otherwise noted.

“*reducing* the total dose [down from 206 mg] in each injection” in order to “reduce adverse effects.” (Ex. 1011 at 1078.)

Similarly misguided is Amneal’s attempt to cobble together the claimed AUC differential via its expert’s hindsight-fueled foray through references that, for good reason, say nothing of AUC and do not support a reasoned calculation of it. (See, e.g., Pet. at 24, 26.) Amneal, no doubt aware of the weaknesses in its AUC analysis, eventually posits that “this limitation should be given little weight.” (Pet. at 31.) The Petition’s slew of missteps do not stop there—its six grounds showcase an assortment of errors: missing claim limitations; failures of proof on motivation to combine and reasonable expectation of success; lack of public accessibility for asserted references, and more. Amneal also ignores compelling objective indicia of nonobviousness of these claims, such as commercial success, skepticism, and industry praise and recognition.

For these reasons and those discussed below, and as further supported by the declarations of Drs. Berkland (Ex. 2055) and O’Brien (Ex. 2056), Amneal has not carried its burden with respect to Grounds 1–6, and the claims should be confirmed.

II. Claim Construction³

The '499 patent's claims should be given their "broadest reasonable construction in light of the specification of the patent in which it appears."

37 C.F.R. § 42.100(b) (2016). Under this standard, a term "generally is given its ordinary and customary meaning," which is the meaning that the term would have to a POSA⁴ at the time of the invention. *Gen. Elec. Co. v. United Tech. Corp.*, IPR2016-00534, Paper 9 at 6–7 (Aug. 12, 2016). Amneal proposes the construction of several claim terms (Pet. at 16–21), without explaining why they require construction, why the Board should depart from their ordinary and customary meaning, or why the proposed constructions are relevant to the alleged grounds for unpatentability.⁵

³ These claim construction arguments are not concessions on the proper scope of any claim term in any future litigation or other patent proceeding.

⁴ A person of ordinary skill in the art 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. (Ex. 2055 ¶ 28.)

⁵ Alkermes does not necessarily agree with any of Amneal's proposed constructions, and it addresses only those that are relevant to the arguments set forth herein.

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

Claim 1 recites a method for treating that comprises “the step of parenterally administering a long acting formulation comprising about 310 mg to about 480 mg of naltrexone.” (Ex. 1001 at 21:3–5.) The broadest reasonable construction of this term, in the context of the ’499 patent, is “a single injection of a long acting formulation comprising about 310 mg to about 480 mg of naltrexone.” (Ex. 2055 ¶ 36.)

This construction is consistent with the words of the claim term, which refer to “*the* step” and “*a* long acting formulation” in singular form. It is also consistent with the ’499 patent’s specification. Example 1 concerns manufacture and does not mention administration (Ex. 1001 at 5:37–8:2), but all of the specification’s other working examples disclose single-injection regimens:

- Example 2 mentions “all 6 injections” (Ex. 1001 at 10 (flow chart)) given over a “6-month treatment period” (*id.* at 14:35). “Patients received an injection of study medication at 4-week intervals over 24 weeks, alternating between the left and right [buttocks].” (*Id.* at 8:41–45.) Injections, occurring at 4-week intervals, were either a single injection of 380 mg long-acting naltrexone, a single injection of 190 mg long-acting naltrexone, or a single placebo injection. (*Id.* at 8:32–44.)

- Example 3 compares meta-analyses on oral naltrexone to the 380 mg dose of the clinical study of Example 2. (*Id.* at 18:40–56.)
- Examples 4 and 5 each refer to “6 monthly injections of LA-NTX [long-acting naltrexone] 380 mg” over a “24-week” period, which a POSA would have understood to disclose a single injection per month for six months. (*Id.* at 19:43–49, 20:8–31.)

In addition, when describing the invention’s unexpected nature, the specification refers to “a single IM administration of Vivitrex®” (*Id.* at 2:34–37). *See Luxshare Precision Indus. Co., Ltd. v. Bing Xu Precision Co., Ltd.*, IPR2017-01404, Paper 51 at 30 (Jan. 10, 2019) (relying on *Toro Co. v. White Consol. Indus., Inc.*, 199 F.3d 1295, 1301–02 (Fed. Cir. 1999), which adopted a claim scope that was consistent with the specification that disclosed a single embodiment and described it as important to the invention).

Moreover, this construction is consistent with the ’499 patent’s prosecution history, where the Ehrich Declaration was relied on by the Examiner in allowing the ’499 patent. (Paper 8 at 10–11.) In particular, the Ehrich Declaration states: “The present invention is directed to the unexpected discovery that *a single injection* of a naltrexone-containing long-acting formulation provides systemic exposure to naltrexone (AUC) which is at least 2 fold higher over a 28 day period than the AUC of an oral regimen of 50 mg per day over a 28 day period.”

(Ex. 1003 at 1.) Similarly, the Ehrich Declaration further refers to “a single 380 mg injection of naltrexone” (Ex. 1003 at 4, 14.) See *Nike, Inc. v. Mayfonk Athletic, LLC*, IPR2015-00656, Paper 8 at 7 n.4 (Aug. 10, 2015) (citing *Tempo Lighting, Inc. v. Tivoli, LLC*, 742 F.3d 973, 977 (Fed. Cir. 2014) for the proposition that, “even for non-expired patents that return to the PTO, prosecution history may be an important component of intrinsic evidence in construing claims.”).

In sum, the intrinsic record is consistently clear that “the step of parenterally administering a long acting formulation comprising about 310 mg to about 480 mg of naltrexone” refers to “a single injection of a long acting formulation comprising about 310 mg to about 480 mg of naltrexone.” (Ex. 2055 ¶¶ 36–48.)

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

Claim 1 recites administering a long acting formulation “wherein the serum AUC of naltrexone is about three times greater than that achieved by 50 mg/day oral administration.” (Ex. 1001 at 21:6–7.) Under the guise of proposing a claim construction, Amneal lodges an improper indefiniteness attack, alleging “lack of clarity due to Alkermes’ failure to define the AUC of either the claimed formulation or oral dosing.” (Pet. at 18.) As explained below, that attack is misguided and irrelevant. See *10X Genomics, Inc. v. Univ. of Chi.*, IPR2015-01157, Paper 14 at 10 (Nov. 16, 2015) (citing *Vivid Techs., Inc. v. Am. Sci. & Eng’g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999) for the proposition that “only terms

in controversy need to be construed, and only to the extent necessary to resolve the controversy”). To the extent the term is construed and for the basis of this IPR, as Dr. Berkland explains, the broadest reasonable interpretation of “the serum AUC of naltrexone . . . achieved by 50 mg/day oral administration” refers to “a serum AUC of oral naltrexone of about 30 µg h/L.” (Ex. 2055 ¶ 34.)

As an initial matter, there is no definiteness problem here. Regardless of whether the ’499 patent explicitly provides AUC values for the disclosed long-acting formulation or for 50 mg/day oral naltrexone, values for both were presented during prosecution via the Ehrich Declaration (Ex. 1003) and relied on by the Examiner. (Paper 8 at 10–11.) Thus there is “an objective baseline [i.e., approximate AUC for 50 mg/day oral naltrexone] through which to interpret the claims.” *Sonix Tech. Co., Ltd. v. Publ’ns.*, 844 F.3d 1370, 1378 (Fed. Cir. 2017); *see also id.* at 1377 (acknowledging the “require[ment] that a patent’s claims [be] viewed in light of the specification *and prosecution history*”). Such intrinsic evidence should be given priority for claim construction purposes.⁶ (Paper 8 at 10.)

⁶ Dr. Park’s discussion of extrinsic evidence regarding allegedly varying AUC values for 50 mg oral naltrexone is merely an attempt to inject uncertainty where there is none. (*See, e.g.*, Ex. 1030 ¶ 82 (citing Ex. 1039, which is not prior art).)

(Continued. . .)

Thus, this is *not* an instance where claim language “might mean several different things and no informed and confident choice is available among the contending definitions.” *Nautilus, Inc. v. Biosig Instruments*, 134 S.Ct. 2120, 2130 n.8 (2014) (internal citation and quotation marks omitted). “The certainty which the law requires in patents is not greater than is reasonable, having regard to their subject-matter.” *Id.* at 2123.

Nor is there controversy here. Indeed, Dr. Park admits that “a POSA would look at the Ehrich Declaration” for data.⁷ (Paper 8 at 11 (quoting Ex. 1030 ¶ 72).) By way of background, the Ehrich Declaration discloses two separately obtained AUC values for 50 mg/day oral naltrexone: one from Tice (Ex. 1015) and one from

Moreover, if true this discussion casts doubt on Dr. Park’s central premise (i.e., Ex. 1030 ¶ 42) that AUC is solely a function of dose.

⁷ Dr. Park also admits that he is developing a depot naltrexone formulation of naltrexone and working with a pharmaceutical company toward submitting an application to the FDA this summer. (Ex. 2025 at 24:4–27:10.) This product would compete with Vivitrol and may infringe the ’499 patent. Indeed, Dr. Park is not yet sure what the AUC will be of his long acting naltrexone formulation. (Ex. 2025 at 32:12–22.) This admission creates a significant question as to whether Dr. Park is truly offering opinions without bias as an independent expert.

Alkermes’s Clinical Study Report # ALK21-005 (Ex. 1003 at 6–12). It concludes that they “result in similar average daily AUC values” of 27.8 ug h/L and 30.5 ug h/L, respectively. (Ex. 1003 at 4.) Regardless of which of these values is chosen as a comparator for long-acting formulations, Dr. Park asserts that the claimed AUC differential will be satisfied by the asserted art. (Ex. 1030 ¶ 82, *see also* ¶¶ 72, 74, 81.) If the Board accepts Dr. Park’s dubious AUC calculation,⁸ then Alkermes, for this proceeding only, will not contest that the claimed AUC differential was taught by the prior art. Thus, there is no need to construe this term.

C. “initial oral dose of naltrexone”

Dependent claim 11 recites that the “individual does not receive an initial oral dose of naltrexone.” (Ex. 1001 at 22:8–9.) In cases where the “the ordinary meaning of claim language as understood by a person of skill in the art may be readily apparent . . . general purpose dictionaries may be helpful.” *Phillips v. AWH Corp.*, 415 F.3d 1303, 1314 (Fed. Cir. 2005) (*en banc*); *see also Trivascular, Inc. v. Samuels*, 812 F.3d 1056, 1062 (Fed. Cir. 2016). Here, the ordinary and customary meaning of “initial” is simply “first.” (Ex. 2054 at 643.) A POSA would

⁸ As explained below, Dr. Park’s attempt to divine an AUC value from the asserted references is fatally flawed for various reasons. (See *e.g.*, §§ III.A.2.a.–d., III.B.2., *infra*.)

therefore understand “initial oral dose of naltrexone” to mean “any oral dose of naltrexone prior to the parenteral administration of a long acting formulation comprising about 310 mg to about 480 mg of naltrexone.” (Ex. 2055 ¶ 53.) Such an understanding is consistent with the claims and the ’499 patent’s specification. (See, *e.g.*, Ex. 1001 at 2:49–53 (“[T]he inventions also include administering a long acting formulation to individuals who did not receive a prior oral dose of naltrexone, for example, within 3, such as within about 5 days or about 10 days of commencing therapy.”).)

Amneal’s and Dr. Park’s proposed construction is misguided. (Ex. 2055 ¶¶ 50–52.) During cross-examination, Dr. Park was evasive and suggested consulting a dictionary regarding the meaning of “initial.” (Ex. 2025 at 53:9–62:22.) That definition, however, is consistent with Dr. Berkland’s construction of “initial oral dose of naltrexone.” (Ex. 2055 ¶ 53.) Dr. Park could not identify any intrinsic evidence that suggests departing from the term’s ordinary and customary meaning. (Ex. 2025 at 56:12–60:20.)

Moreover, Dr. Park’s argument for limiting “initial oral dose” to exclude dosing for detoxification is incomprehensible. Dr. Park relies primarily on Comer for his construction of excluding prior initial oral doses for detoxification (Ex. 1030 ¶ 49), but Comer only administers an initial oral dose precisely for detoxification. (Ex. 1010 at 353.) Having relied on Comer for the exact opposite of

what it teaches, predictably, Dr. Park then asserts that Comer meets this claim limitation since its initial oral dose is for detoxification, not for treatment.

(Ex. 1030 ¶ 93.) This makes no sense.

III. Amneal Has Not Established Anticipation

Establishing anticipation requires rigorous proof. *See Motorola, Inc. v. Interdigital Tech. Corp.*, 121 F.3d 1461, 1473 (Fed. Cir. 1997). “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., Inc. v. Union Oil Co. of Cal.*, 814 F.2d 628, 631 (Fed. Cir. 1987). Moreover, the reference must enable those skilled in the art to make and use the claimed invention without undue experimentation. *PPG Indus. v. Guardian Indus. Corp.*, 75 F.3d 1558, 1566 (Fed. Cir. 1996).

Extrinsic evidence may be used to explain—not expand—the meaning of a reference. *In re Baxter Travenol Labs.*, 952 F.2d 388, 390 (Fed. Cir. 1991). Though it may be permissible to “use . . . additional references to interpret the allegedly anticipating reference,” *Studiengesellschaft Kohle, m.b.H. v. Dart Indus., Inc.*, 726 F.2d 724, 727 (Fed. Cir. 1984), the additional reference “must make clear that the missing descriptive matter is *necessarily* present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill.” *Cont’l Can Co. USA Inc. v. Monsanto Co.*, 948 F.2d 1264, 1268 (Fed. Cir. 1991)

(quoting *Hansgirg v. Kemmer*, 102 F.2d 212, 214 (Fed. Cir. 1991) (“Inherency . . . may not be established by probabilities or possibilities.”)).

Here, Amneal has failed to show that either allegedly anticipatory reference discloses each and every limitation of the contested claims. For example, neither Comer nor Nuwayser discloses the step of parenterally administering a long-acting single injection formulation comprising about 310 mg to about 480 mg of naltrexone or the claimed AUC limitation. Comer further fails to disclose a method of “treating,” while Nuwayser further fails to disclose the claimed range of doses. Therefore Amneal has not carried its burden with respect to Grounds 1 and 2, and the claims should be confirmed.

A. Ground 1: The Claims Are Not Anticipated by Comer

1. Comer Does Not Disclose a Single Injection of Naltrexone Within the Claimed Range of Doses

As discussed above, Comer reports mean plasma levels for two doses of depot naltrexone: 192 mg and 384 mg. For the lower dose, study participants received “one placebo and one naltrexone injection.” (Ex. 1010 at 354.) For the higher dose, they received “two naltrexone injections.” (*Id.*) Therefore Comer does *not* disclose “the step of parenterally administering a long acting formulation” of naltrexone within the claimed range of doses (i.e., “about 310 mg to about 480 mg”), as properly construed to refer to “a *single* injection of a long acting

formulation comprising about 310 mg to about 480 mg of naltrexone.” (See § II.A., *supra*.)

2. Comer Does Not Disclose the Claimed AUC Differential

Comer does not explicitly report AUC or the claimed AUC differential.⁹ Therefore Amneal’s allegation of anticipation over Comer (i.e., Ground 1) hinges on the assumptions that a POSA could have arrived at the claimed AUC differential by (i) obtaining an AUC value from Comer’s Figure 1 (Ex. 1010 at 354) and then (ii) comparing that AUC value to data presented in either the Ehrich Declaration (Ex. 1003 at 6) or the Tice patent (Ex. 1015 at 14:34–58). (Pet. at 24.) However, as explained below, a POSA would not have attempted to obtain an AUC from Comer because it has fatal flaws that would have been readily apparent to a POSA.

By way of background, Comer’s Figure 1 depicts a series of mean plasma levels of naltrexone (left panel) and its metabolite (right panel). (Ex. 1010 at 354.) These plots reflect measurements taken hours after administration of the naltrexone

⁹ When Dr. Park was asked, “Can you see the word ‘AUC’ anywhere in [Ex. 1010]?” Dr. Park was evasive and ultimately said, “No.” (Ex. 2025 at 88:15–91:5.) Not only is AUC not explicitly reported, but a POSA would not attempt to determine an AUC from Figure 1. (See §§ III.A.2.a.–d., *infra*.)

depot. They do not provide any information regarding the days prior to depot administration, during which study participants were administered a three-day regimen of oral naltrexone (daily doses of 25, 50, and 50 mg) (*Id.* at 353.) Depot naltrexone was administered “2 days after the last oral naltrexone dose.” (*Id.*)

Following administration of depot naltrexone, blood samples were drawn from each participant after 2 hours, and then again after 1, 2, 3, 4, 5, 6, 8, 11, 15, 18, 22, 25, 29, 32, 36, and 39 days. (*Id.* at 354.) Comer measured plasma levels of naltrexone and its metabolite and determined a mean value, for each of the two doses, at each time point. The resulting series of mean values were then plotted in Figure 1 to depict plasma level of naltrexone as a function of time. (*Id.*) Relying on Figure 1, Amneal incorrectly alleges that a POSA would have understood Comer to disclose the claimed AUC differential.

a) AUC calculations must begin from time zero.

As an initial matter, a POSA would have known that attempts to quantify AUC must begin “from time zero.” (Ex. 2055 ¶ 59 (citing Ex. 1045 at 9); *see also* Ex. 2026 at 6; Ex. 1044 at 263 (“It is imperative in single-dose studies . . . to determine the AUC from time zero to infinity.”).) Dr. Park agrees. (Ex. 2025 at 67:4–5 (“PK profile must start from time zero.”).) But Comer’s blood draws began two hours after depot administration. (Ex. 1010 at 354.) Therefore a POSA would have immediately recognized that Comer’s incomplete data set does not

show “a whole picture of the pharmacokinetic profile” (Ex. 2025 at 66:23–67:5) and is unacceptable for determining pharmacokinetic variables such as AUC (Ex. 2055 ¶ 59). A POSA simply would have had no way to adequately quantify AUC without knowing the rate and extent of changing plasma levels surrounding the two-hour time point. (Ex. 2055 ¶¶ 59; 62–63.) Consistent with this conclusion, Comer itself does not explicitly report AUC, $C_{\max}$, or $T_{\max}$ based on its data.

b) AUC calculations should not be based on data that begins with $C_{\max}$.

A POSA also would have found Comer to be unacceptable for determining pharmacokinetic variables such as AUC because the highest plasma concentration depicted in Figure 1 was obtained upon the first blood draw. (Ex. 2055 ¶ 60.) FDA Guidance for Industry refers to this phenomenon as “first-point $C_{\max}$ ” and recognizes it as a “problem” because it reflects “insufficient early sampling times” and “raises questions” that may undermine inferences from concentration measurements. (*See, e.g.*, Ex. 1045 at 19; Ex. 2026 at 13.) For example, the sampling depicted in Figure 1 cannot properly support an inference about whether peak plasma levels actually occurred before or after the first blood draw. (Ex. 2055 ¶¶ 60–61.) This is likely another reason why Comer does not explicitly report pharmacokinetic variables such as $C_{\max}$, $T_{\max}$, and AUC. (*Id.*)

For data sets affected by first-point $C_{\max}$ to nevertheless be “considered adequate,” the FDA Guidance for Industry makes clear that sampling should occur

early and often after administration. (*See, e.g.*, Ex. 1045 at 19–20 (suggesting that samples be taken within 5–15 minutes after administration and several times over the first day); *see also* Ex. 2026 at 13.) A POSA would have understood this principle to be generally true of non-intravenous formulations, such as oral and depot formulations. (Ex. 2055 ¶ 61.) In light of known problems with Comer’s measurements, such as first-point $C_{\max}$, a POSA would not have relied on Figure 1 to determine pharmacokinetic variables such as AUC. (*Id.* ¶ 60.)

c) AUC calculations require frequent sampling.

A POSA also would have recognized that Comer’s blood draws were not “frequent enough so that curvature of the plasma concentrations between [consecutive] data points is negligible,” as is “require[d]” for approximation of AUC. (Ex. 2055 ¶ 62 (quoting Ex. 1044 at 262).) Dr. Park agrees that “measuring as many as possible time points in a first day or two is critically important.” (Ex. 2025 at 79:25–80:2.) Again, Comer’s lack of sufficiently early and frequent measurements are part of the reason why a POSA would not have relied upon Figure 1 to quantify the early release and (unreported) pharmacokinetic variables such as AUC. (Ex. 2055 ¶ 63.)

In addition, a POSA would have understood that Comer lacks sufficient data from the second week after depot administration. (*Id.* ¶¶ 63–65.) For example, Figure 1 depicts a second spike in plasma levels of naltrexone between the eighth

and fifteenth days after depot administration, during which its researchers took only one blood draw from study participants. (*Id.* ¶ 63; Ex. 1010 at 354.) A POSA would have viewed that second-week spike as indicating the need for additional studies—with more frequent sampling—in order to adequately report pharmacokinetic variables such as AUC. (Ex. 2055 ¶¶ 62, 65.)

Where there is non-negligible change in curvature between consecutive data points in a plasma-concentration plot, a POSA would have known that simply connecting those points with a straight line¹⁰ and then attempting to calculate the area underneath them would result in erroneous AUC estimates. (*Id.* ¶ 64 (citing Ex. 1044 at 262, which explains why such an approach would lead to erroneous AUC determinations).) A POSA would have recognized Comer's Figure 1 as depicting non-negligible changes during or around the second week after Comer's depot administration. (*Id.* ¶ 63.) For example, Figure 1 suggests that a spike occurred during the second week after depot administration. (*Id.* ¶¶ 63, 65.) The precise time that this spike occurred and the true shape of the curve surrounding the spike are unknown. (*Id.* ¶¶ 63–65.) Therefore a POSA, recognizing the

¹⁰ A POSA would have understood that Comer's use of straight lines to connect consecutive data points is merely meant to aid readers in easily distinguishing the two sets of data points plotted on the same coordinate plane. (Ex. 2055 ¶ 64.)

likelihood of introducing error, again would not have tried to rely on Figure 1 to determine AUC. (*Id.* ¶ 65.)

d) An AUC calculation should rule out contamination from the prior oral dosing.

A POSA also would have understood Figure 1 to be deficient for calculating AUC for depot naltrexone because Comer fails to rule out the potentially contaminating influence¹¹ of previously administered oral naltrexone. (*Id.* ¶¶ 66–68.) Indeed, Comer failed to take a blood draw until two hours *after* depot injection, despite the fact that study participants had completed a three-day regimen of oral naltrexone (25, 50, and 50 mg per day) just two days before receiving the depot. (Ex. 1010 at 353–54.) Knowing that Figure 1 fails to rule out the influence of oral naltrexone, a POSA would have recognized the impossibility of attributing to the depot formulation alone the plasma levels reflected in Figure 1. (Ex. 2055 ¶ 68) Since the prior art taught that a single 50 mg tablet of naltrexone can exhibit a half-life of over 14 hours (*see, e.g.*, Ex. 2028 at 18), a POSA would not have ruled out the presence of oral naltrexone from the series of mean plasma levels depicted in Figure 1. (Ex. 2055 ¶ 68.)

¹¹ During his deposition, Dr. Park cited to Hamilton (Ex. 2030), which illustrates the use of a time-zero blood draw to ensure washout (i.e., that previously administered drug is no longer present). (Ex. 2055 ¶ 67 n.8.)

For all of these reasons, a POSA would have recognized the need for further studies before attempting to determine the AUC of the “Depotrex” used in the Comer study. As such, Amneal cannot establish facts supporting its challenge by a preponderance of the evidence. 35 U.S.C. § 316(e); 37 C.F.R. § 42.1(d)).

3. Comer Does Not Disclose “Treating”

Comer is a self-described study regarding the possibility that a depot naltrexone can antagonize the effects of heroin. (Ex. 1010 at 351 (Abstract).) It does *not* disclose the claim limitation, “*treating* an individual in need of naltrexone.” (*Id.*) The Institution Decision states that Comer “discloses administering naltrexone to opioid-dependent *patients*, and discloses that naltrexone is a *treatment* for heroin dependence.” (Paper 8 at 21.) Alkermes respectfully disagrees.

Importantly, Comer expressly discloses that “[p]articipants were *excluded from the study if they were seeking drug treatment.*” (Ex. 1010 at 352.) That disclosure alone should put to rest any question as to whether Comer discloses treatment; Comer does not. Without once referring to “patients” being “treated,” Comer consistently refers to individuals receiving naltrexone as “participants” for “test[s].” (See, e.g., Ex. 1010 at 354 (“the low dose of Depotrex was tested in the first six participants, and the high dose of Depotrex was tested in the next six participants”).)

Especially in light of the fact that study participants received “[a]ctive heroin doses . . . administered in ascending order” (Ex. 1010 at 351 (Abstract)), a POSA would have recognized that Comer does not teach “treating.” (Ex. 2056 ¶¶ 19–22.) One does not treat heroin addiction by giving the addicts more heroin. (*Id.* ¶ 19.) Instead, a POSA would have recognized that Comer merely tests whether depot naltrexone can antagonize the effects of heroin (a condition that may be necessary, but may be insufficient for treatment). (*Id.* ¶ 20.) Only “during the last week of the study” were Comer’s participants “offered *referrals* for treatment.” (Ex. 1010 at 353.)

Though Comer concludes that depot naltrexone “provides a safe, effective, long-lasting antagonism of the effects of heroin,” that refers to a pharmacologic effect: the ability to block opioid receptors. (Ex. 1010 at 351.) A POSA would not have interpreted it to refer to the overall effectiveness that a POSA would have associated with “treating.” (Ex. 2056 ¶¶ 20–21.) And while Comer also states that its findings have “important and exciting treatment *implications*,” it specifies that evaluations of “the clinical utility of depot naltrexone in the treatment of heroin dependence” would take place in “[f]uture studies.” (Ex. 1010 at 359.) From such statements, a POSA would have understood that Comer itself recognized the need for more information before forming any to conclusions about whether the tested formulations could be useful for actually “treating” patients. (Ex. 2056 ¶¶ 20–21.)

a) Amneal Has Not Shown 1 ng/mL To Be Sufficient for “Treating”

Amneal insists that Comer’s depot formulations provided plasma levels of naltrexone “above the *therapeutic* level of 1 ng/mL” (Pet. at 23). This allegation appears to be rooted in Amneal’s unfounded belief that “any way of maintaining therapeutic blood levels of naltrexone of at least 1 ng/ml will be effective [presumably, for treatment].” (Pet. at 2.) Similarly, Amneal alleges that “[a]ny of the prior art formulations that provide at least 1 ng/ml/day serum levels should be therapeutically effective (if used correctly).” (Pet. at 12 (citing Ex. 1030 ¶¶ 54, 60).) Amneal’s attempt to support such assertions is convoluted, apparently hinging on Dr. Park’s *unsupported* statement that, “[s]o long as a formulation, whether oral or parenteral, provided this minimum therapeutic concentration [i.e., at or above 1 ng/mL] over the desired dosing interval, the treatment should be effective.”¹² (Ex. 1030 ¶ 60.)

Even if Dr. Park’s statement were meant to draw support from evidence discussed in nearby-cited Paragraphs 52–55, it still must fail. Indeed, Paragraph 52

¹² Dr. Park is not a medical doctor and therefore of course has not treated any patient for any condition. (See Ex. 2025 at 84:2–6; Ex. 1030 ¶ 108.)

addresses the 1 ng/mL value, citing Exhibits 1010, 1011, 1012, 1013, and 1015, none of which support Dr. Park's claim:¹³

1. Comer tests heroin-dependent men and reports that plasma levels above 1 ng/mL effectively antagonized heroin, but it offers no conclusion about therapeutic effect. (Ex. 1010 at 351.)
2. Kranzler tests alcohol-dependent men and women and states that naltrexone "in excess of 1 ng/mL . . . can be expected to block opioid agonist effects," but it does not report any *degree* of blockade, let alone a therapeutic one. (Ex. 1011 at 1078.)
3. Alim tests cocaine-dependent men and reports (i) that plasma levels of 1 ng/mL were associated with "[o]piate receptor blockade . . . *although physiologic and subjective responses were variable,*" and (ii) that "[h]igher doses . . . may better assess efficacy." (Ex. 1013.)
4. Chiang (1984) tests healthy, normal men and reports that 2 ng/mL provided "[n]early complete narcotic antagonism," but then speculates that "minimum effective concentration of naltrexone for the treatment of opiate addiction may be lower than 1 ng/mL." (Ex. 1025 at 704.)

¹³ Since other parts of the Petition cite these references alongside Exhibits 1019 and 1025 (*see, e.g.*, Pet. at 11), this list addresses those as well.

5. Chiang (1985) tests healthy, normal men and suggests 1 ng/mL as a “*minimum* effective plasma level,” which at best suggests such levels are *necessary*, as opposed to *sufficient*, for treatment. (Ex. 1012 at 7.)
6. Heishman tests healthy individuals and reports normal laboratory results with no adverse effects from 0.93 ng/mL, but says nothing of therapeutic effect and indicates that further tests will seek “to achieve a sustained naltrexone plasma concentration of 1-2 ng/mL.” (Ex. 1019.)
7. Tice refers generally to “heroin addicts” and “alcoholics,” and states that levels of 2 ng/mL are “more preferabl[e]” than 1.5 ng/mL or 1.0 ng/mL for “protection” (from what is unclear) and to “inhibit response to a 50-mg challenge dose of heroin or an equivalent dose of a different drug.” (Ex. 1015 at 6:19–39.)

In sum, this hodgepodge of references cannot support Dr. Park’s (non-medical) assertion regarding the alleged therapeutic effect of 1 ng/mL naltrexone. (See Ex. 2056 ¶ 21.) In addition, more recent prior art (not cited by Amneal or Dr. Park) recognizes 2 ng/mL as the “minimum therapeutic range” required “to develop an acceptable and effective sustained-release formulation of naltrexone.” (Ex. 2010 at 1980 (citing Ex. 2038 at 156 (“The lowest effective naltrexone plasma

level was 2.0 ng/ml Thus, in therapy for effective opiate antagonistic activity, plasma levels of 2.0 ng/ml or greater should be maintained.”)).)

B. Ground 2: The Claims Are Not Anticipated by Nuwayser

Despite concerns over Amneal’s flawed logic, the Board instituted Ground 2 “[i]n light of SAS and USPTO Guidance.” (Paper 8 at 27.) As explained below, Nuwayser does not anticipate the contested claims.

1. Nuwayser Does Not Disclose a Single Injection of Naltrexone Within the Claimed Range of Doses

As an initial matter, Nuwayser does not disclose the claimed range of doses. See § III.B.3., *infra*. Moreover, the title of Nuwayser’s Figure 7 confirms that the higher dose depicts “double [subcutaneous] injections.” (Ex. 1014.) Therefore Nuwayser does *not* disclose “the step of parenterally administering a long acting formulation” of naltrexone within the claimed range of doses (i.e., “about 310 mg to about 480 mg”), as properly construed to refer to “a *single* injection of a long acting formulation comprising about 310 mg to about 480 mg of naltrexone.” (See § II.A., *supra*.)

2. Nuwayser Does Not Disclose the Claimed AUC Differential

Nuwayser’s Figure 7 suffers from various deficiencies as discussed with respect to Comer’s Figure 1. (Ex. 2055 ¶ 78.) A POSA would not have relied on either to determine AUC or the claimed AUC differential. (See § III.A.2., *supra*.)

3. Nuwayser Does Not Disclose the Claimed Range of Doses

The Board correctly notes that “Nuwayser does not teach expressly the claimed dosage range” of about 310 mg to about 480 mg of naltrexone. (Paper 8 at 26.) Amneal’s arguments to the contrary are deficient. Amneal attempts to circumvent that fact by circularly alleging that because Comer’s Figure 1 and Nuwayser’s Figure 7 are superimposable, their doses must be the same, and because their doses are the same, their AUCs are the same. (See Paper 8 at 27 (referring to Pet. at 26–27).) The Board correctly pointed out the circularity of such logic. (Paper 8 at 27.) Besides, contrary to Amneal’s arguments, “the pharmacokinetic profile of naltrexone long acting microspheres is dependent on the dose *and* formulation” (Ex. 1027 at 6), meaning dose cannot be derived from AUC alone. (Ex. 2055 ¶ 80.)

C. At a Minimum, Dependent Claims 10 and 11 Are Not Anticipated

The Board aptly questioned whether Amneal properly challenged claims 10 and 11 for anticipation. (Paper 8 at 25.) Amneal did not. As explained in Sections III.A. and III.B., *supra*, Comer and Nuwayser each fail to disclose all features of claim 1, from which claims 10 and 11 depend. They should be confirmed for at least that reason. In addition, as explained below, claims 10 and 11 recite additional features that are not disclosed in Comer or Nuwayser.

1. Claim 10: Comer Does Not Disclose Administration to an Individual Afflicted by Alcohol Dependency

Dependent claim 10 recites administration of a long-acting formulation to “an individual afflicted by alcohol dependency.” (Ex. 1001 at col. 22:6-7.) Amneal challenged this claim as anticipated by Comer but not Nuwayser. (Pet. at 4.) Comer’s study protocol, however, discloses administration of depot naltrexone solely to “heroin-dependent individuals.” (Ex. 1010 at 351.) In fact, Comer expressly discloses that “[p]articipants were excluded from the study if they were . . . dependent on alcohol.” (Ex. 1010 at 352.) Therefore a POSA would not have understood Comer to teach administration to individuals afflicted by alcohol dependency. (Ex. 2055 ¶¶ 71–72.)

Amneal’s anticipation challenge to claim 10 hinges on Comer’s discussion of Kranzler (Ex. 1011), which purportedly shows that “206 mg depot naltrexone” “appears to be safe and effective in treating alcohol dependence.” (Ex. 1010 at 352.) The claimed methods, however, recite a formulation comprising “about 310 mg to about 480 mg of naltrexone” (Ex. 1001 at 21:4–5), meaning a POSA would have recognized the purportedly effective dose to be about 33% less than the low end of the range claimed in the ’499 patent.¹⁴ (Ex. 2055 ¶ 72.) Amneal fails

¹⁴ Dr. Park opines that the claim term “about” covers quantities “within 10%.” (Ex. 1030 ¶ 47.)

to provide any explanation for how a POSA might nevertheless interpret Comer to disclose administration of the claimed dose range to individuals afflicted by alcohol dependency. For at least this reason, Comer does not anticipate claim 10.

2. Claim 11: Neither Comer nor Nuwayser Disclose Administration Without an Initial Oral Dose

Dependent claim 11 requires that the claimed individual in need of naltrexone “does not receive an initial oral dose of naltrexone.” (Ex. 1001 at 22:8–9.) Yet Comer makes clear that study participants each underwent “detoxification,” during which they were administered oral naltrexone once daily for three consecutive days (25 mg, 50 mg, and 50 mg per day) shortly before administration of depot naltrexone. (Ex. 1010 at 353.) Amneal attempts to distinguish that sequence of oral doses, arguing that it “was not an ‘initial’ treatment dose, as it was given for other purposes.”¹⁵ (Pet. at 25.)

Amneal’s argument is misguided. As discussed in Section III.A.3., *supra*, Comer does not teach treating. Besides, the plain language of claim 11 (*see* § II.C., *supra*) excludes methods wherein individuals receive an initial oral dose of naltrexone, whatever the reason. (Ex. 2055 at ¶ 53.) In sum, Comer’s study participants received oral naltrexone prior to depot naltrexone, meaning Comer falls outside the scope of claim 11 and does not anticipate it.

¹⁵ *See* § II.C., *supra* (regarding the illogic of Amneal’s claim construction.)

Nor does Nuwayser anticipate claim 11. Nuwayser simply fails to disclose a protocol, let alone one in which the “individual does not receive an initial oral dose of naltrexone.”¹⁶

IV. Amneal Has Not Established Obviousness

A claim is unpatentable under 35 U.S.C. § 103 if the differences between the patented subject matter 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 POSA. *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). Obviousness is a question of law based on underlying factual findings, including: (1) the scope and content of the prior art; (2) the differences between the claims and the prior art; (3) the level of ordinary skill in the art; and (4) objective indicia of nonobviousness. *Graham v. John Deere Co. of Kan. City*, 383 U.S. 1, 17-18 (1966).

The obviousness analysis “entails consideration of whether a [POSA] would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and . . . would have had a reasonable expectation of success in doing so.” *Insite Vision Inc. v. Sandoz, Inc.*, 783 F.3d 853, 859 (Fed. Cir. 2015)

¹⁶ To the extent that Nuwayser allegedly discloses a protocol, Dr. Park suggests that a POSA would have understood it to be the same as Comer’s, and therefore would have likewise involved initial oral doses of naltrexone. (Ex. 1030 ¶ 90.)

(internal quotation omitted). The Federal Circuit instructs that “all evidence relevant to obviousness or nonobviousness be considered, and be considered collectively,” without resort to presumptions of *prima facie* obviousness or burden-shifting. *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1078–79 (Fed. Cir. 2012); *see also Intri-Plex Techs., Inc. v. Saint-Gobain Performance Plastics Rencol Ltd.*, IPR2014-00309, Paper 83 at 45–46 (Mar. 23, 2015).

As explained below, Amneal has not made the requisite showing. Therefore Amneal has not carried its burden with respect to Grounds 3–6, and the claims should be confirmed.

A. Amneal’s Obviousness Grounds Rely on Improper Hindsight

“Importantly, the great challenge of the obviousness judgment is proceeding without any hint of hindsight.” *Star Scientific, Inc. v. R.J. Reynolds Tobacco Co.*, 655 F.3d 1364, 1375 (Fed. Cir. 2011); *see also Cheese Sys., Inc. v. Tetra Pak Cheese & Powder Sys., Inc.*, 725 F.3d 1342, 1352 (Fed. Cir. 2013) (“Obviousness cannot be based on the hindsight combination of components selectively culled from the prior art to fit the parameters of the patented invention.”) (internal citations and quotation marks omitted).

In particular, “reference to ‘routine testing’ or ‘routine experimentation’ is disfavored.”¹⁷ *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1367 (Fed. Cir. 2007). The Federal Circuit has reversed findings of obviousness, even in instances where it was arguably obvious “to experiment with” certain parameters, when there was “nothing to indicate that a skilled artisan would have had a reasonable expectation that such an experiment would succeed in being therapeutically effective.” *In re Cyclobenzaprine*, 676 F.3d at 1070.

Accordingly, the Board has rejected arguments alleging obviousness of pharmaceutical formulations based on hindsight analysis. *See, e.g., Purdue Pharma LP v. Depomed, Inc.*, IPR2014-00378, Paper 73 at 26–28 (July 8, 2015) (citing *Insite* and rejecting petitioner’s reliance on “impermissible hindsight to supply the reason to combine” references asserted against formulation claims); *Endo Pharms., Inc. v. Depomed, Inc.*, IPR2014-00652, Paper 68 at 19 (Sept. 16, 2015) (“[W]e must be careful not to allow hindsight reconstruction of references to reach the claimed [formulation] without any explanation as to how or why the reference would produce the claimed [formulation].”); *Coal. For Affordable Drugs*

¹⁷ For example, the Petition posits that, “[i]t would require nothing more than routine experimentation to prepare an AUC-dose standard curve to find a dose for any given AUC.” (Pet. at 40.)

XI LLC v. Insys Pharma, Inc., IPR2015-01800, Paper 9 at 5 (Mar. 10, 2016)

(criticizing a petition’s “failure to identify a persuasive reason why a person of ordinary skill in the art would have been prompted to combine the various elements of the prior art in the precise fashion required by the challenged [formulation] claims.”).

As demonstrated below (*see* §§ IV.B.–D., *infra*), Amneal’s proposed grounds are fraught with such hindsight, using the ’499 patent and the challenged claims as a roadmap to stitch together the various references and arrive at its obviousness positions. Generally speaking, Amneal’s arguments hinge on the notion that a POSA would have divined the claimed AUC differential by either (i) attempting to measure AUC from the deficient data set depicted in Comer and Nuwayser, both of which declined to report AUC (Grounds 3–5); or (ii) working backwards from the ’499 patent itself¹⁸ (Ground 6, *see, e.g.*, Pet. at 47 (“It would be readily apparent to a POSA that at least one of these three particles was used in

¹⁸ “It is wrong to use the patent in suit as a guide through the maze of prior art references, combining the right references in the right way so as to achieve the result of the claims in suit.” *Orthopedic Equipment Co., Inc. v. United States*, 702 F.2d 1005, 1012 (Fed. Cir. 1983).

the study of the '499 Patent and would result in the same AUC as identified in the '499 Patent.”)).

As a detailed example, Amneal relies solely on hindsight-based declaration testimony from Dr. Park to support its allegations that Comer discloses the claimed AUC differential. In relevant part, that testimony attempts to reverse-engineer the claimed AUC differential from the series of mean plasma levels depicted in Comer’s Figure 1.¹⁹ That effort is flawed for various reasons. Among them, it relies on a technique not shown to exist in the prior art (i.e., counting pixels with Photoshop, *see* Ex. 1030 ¶ 68) and offers no explanation for bypassing those that allegedly were (Ex. 1030 ¶ 56; Ex. 2055 ¶¶ 82–83).²⁰ It also fails to address

¹⁹ For reasons previously discussed, a POSA would *not* have attempted to do the same. (*See* §§ III.A.2. and III.B.2., *supra*.)

²⁰ Alkermes and its declarant, Dr. Berkland, are aware of no peer-reviewed references, in the relevant timeframe, that employ Photoshop to determine a reported AUC. (Ex. 2055 ¶¶ 82–83.) When asked to identify any such reference at his deposition, Dr. Park identified Hamilton 2009 (Ex. 2030), presumably located by Dr. Park in response to the criticisms of his analysis in Patent Owner’s Preliminary Response. (Paper 7 at 21–23.) Assuming this is the best Dr. Park could locate, identification of Hamilton 2009 highlights the failings of using Photoshop (Continued. . .)

whether versions of Photoshop in existence at the time of invention (if any) had the ability to count pixels.²¹ (Ex. 1030 ¶¶ 67–77.)

Though Dr. Park generically alleges that “computer program[s]” would have been available to a POSA, his alleged support identifies only those “designed for pharmacokinetic modeling . . . , such as NONLIN,” and *not* Photoshop. (Ex. 1044 at 263.) Unlike Dr. Park’s counting of pixels under a series of mean data points that are arbitrarily connected by straight lines, NONLIN determines AUC by properly fitting a curve to data measured from individual patients and then mathematically integrating the area under that curve. (Ex. 2055 ¶ 83.)

In sum, Amneal relies on far more than a hint of hindsight. Amneal’s obviousness allegations should be rejected for this reason alone.

to determine a reported AUC. First it was not available to a POSA at the time of invention. Second, Photoshop was not employed to determine a reported pharmacokinetic AUC value, rather Hamilton employs the conventional “linear trapezoid method” for this. (Ex. 2030 at 46.)

²¹ When asked about Photoshop during his deposition, Dr. Park was unable or unwilling to shed light on its use: “Oh, I don’t recall. I just use a program.” (See Ex. 2025 at 95:5–96:15.) Dr. Park also testified that he could not remember the last time he personally calculated an AUC. (*Id.* at 70:6–71:5.)

B. Grounds 3 & 4: The Claims Are Not Obvious Over Comer, Nuwayser, Rubio, and Wright

Grounds 3 and 4 are “identical, but switch[] the primary and secondary references.” (Pet. at 36.) They attempt to rely on Comer and Nuwayser “as those references are described in Grounds 1 and 2.” (Pet. at 29.) In addition, Amneal attempts to rely on Rubio (Ex. 1028) with respect to claims 2, 6, and 10 because, according to Amneal, “Rubio teaches that treatment protocols of 12 months in alcoholics were known.” (Pet. at 33; *see also id.* at 34, 54–56.) Amneal also attempts to rely on Wright (Ex. 1018) with respect to claim 13 because, according to Amneal, Wright shows that “[i]t was well-known that drug loading could be in the range of 30-75% by weight of the formulation.” (Pet. at 36, 39, 57.)

As explained below, the combination of Comer, Nuwayser, Rubio, and Wright does not render obvious the contested claims.

1. The Asserted Combination Does Not Disclose a Single Injection of Naltrexone Within the Claimed Range of Doses

The Board correctly observes that, under *KSR*, “A claim is unpatentable under 35 U.S.C. § 103 if the differences between the claimed subject matter and the prior art are such that the subject matter, as a whole, would have been obvious at the time of the invention to a person having ordinary skill in the art.” (Paper 8 at 27–28 (citing *KSR*, 550 U.S. at 406).) Yet nothing in *KSR* authorizes findings of obviousness when fewer than all of the claim features are disclosed in the prior art.

See, e.g., K/S HIMPP v. Hear-Wear Techs., LLC, 751 F.3d 1362, 1366 (Fed. Cir. 2014) (“In contradistinction to *KSR*, this case involves the lack of evidence of a specific claim limitation, whereas *KSR* related to the combinability of references where the claim limitations were in evidence.”). None of the asserted references discloses parenteral administration, let alone a single injection of naltrexone within the claimed range of doses. (Ex. 2055 ¶ 85.) Thus, the asserted combination fails to meet this claim limitation for the same reasons discussed in Sections III.A.1. and III.B.1., *supra*.

2. The Asserted Combination Does Not Disclose the Claimed AUC Differential

As discussed above, Comer and Nuwayser do not disclose AUC, let alone the claimed AUC differential.²² (*See* §§ III.A.2. and III.B.2., *supra*.)

3. A POSA Would Not Have Been Motivated or Had a Reasonable Expectation of Success in Combining the Asserted References

A POSA seeking additional information on Comer’s depot formulation would turn to the references that Comer specifically identifies as pertinent: Kranzler (Ex. 1011), Alim (Ex. 1013), and Heishman (Ex. 1019). (Ex. 1010 at 352; Ex. 2055 ¶¶ 54, 86.) Amneal has failed to establish that a POSA without the

²² Amneal relies on Rubio (Ex. 1028) and Wright (Ex. 1018) with respect to other claim terms.

benefit of hindsight would have instead sought information from the later-filed patent application that gave rise to Nuwayser (Ex. 1014). (Pet. at 22 n.3.)

In any event, Amneal must demonstrate “not only . . . that prior art elements are capable of being physically combined, but also that the combination would have worked for its intended purpose.” *DePuy Spine Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009). “Importantly, without a sound explanation for doing otherwise, . . . the expectation-of-success analysis must match the highly desired goal, not switch to a different goal that may be a less challenging but also less worth-while pursuit.” *Institut Pasteur & Universite Pierre Et Marie Curie v. Focarino*, 738 F.3d 1337, 1346 (Fed. Cir. 2013).

Amneal has failed to establish that a POSA would have had a reasonable expectation of success in achieving the purpose of the claims: treatment using a single injection of a long-acting formulation of naltrexone that provides an AUC about three times greater than that achieved by 50 mg/day oral administration. (See, e.g., Ex. 1001 at 1:31–39.) Instead, Amneal takes the approach that is expressly prohibited by *Institut Pasteur*, arguing (i) that the claimed AUC differential “would not be expected to have a meaningful impact on efficacy,” and (ii) that, “[s]o long as therapeutic blood levels were maintained, . . . the treatment should be equally effective no matter how much higher the blood concentration, i.e., the AUC.” (Pet. at 31–32 (regarding Ground 3); Pet. at 36 (indicating that any

differences between Grounds 3 and 4 “only really impact[] the motivation” to combine).)

4. At a Minimum, Dependent Claims 2, 6–9, and 11 Are Not Obvious Over Comer, Nuwayser, Rubio, and Wright

a) Claims 2 & 6: The Asserted Combination Does Not Teach Administering Every Four Weeks Or For a Period of About 24 Weeks or More

Dependent claims 2 and 6 recite treatment lasting “every four weeks for a period of about 24 weeks or more” and “over a period of about 24 week period or longer,” respectively. (Ex. 1001 at 21:10–14, 23–25.) Attempting to satisfy these claim limitations, Amneal points to Comer’s mention of “chronic administration of over 1 year”²³ (Ex. 1010 at 351) and Rubio’s use of a 12-month trial protocol (Ex. 1028 at 419). (Pet. at 33–34, 54, 55.) Both disclosures concern oral dosing and make no mention of long-acting, parenterally administered, 310–480 mg formulations such as those claimed in the ’499 patent. (Ex. 2024 at 67; Ex. 1028

²³ For this point, Comer cites Kleber 1985 (Ex. 2024), which discloses oral administration. (Ex. 2024 at 67; Ex. 2025 at 113:18–114:6.) In addition, contrary to what Dr. Park states (Ex. 1030 ¶ 111), Comer refers to “chronic administration” not “chronic treatment” (Ex. 1010 at 351). At his deposition, Dr. Park admitted that none of Comer, Kleber, or Rubio discloses administration “every four weeks for a period of about 24 weeks.” (Ex. 2025 at 112:24-116:10.)

at 420.) Neither reference discloses administration every four weeks. (Ex. 2055 ¶ 90.) Moreover, it does not make sense to combine Comer's administration of depot injectable naltrexone to heroin addicts with a protocol (Rubio) intended for oral dosing of alcoholics.

Critically absent from the Petition is any explanation of why a POSA might have reasonably expected success in combining Comer, Nuwayser, Rubio, and Wright to achieve claims 2 and 6. Indeed, the prior art contains various examples of prolonged drug exposure leading to drawbacks relative to shorter exposures. (Ex. 2055 ¶ 89.) Amneal has not explained why a POSA would have expected to be able to administer long-acting naltrexone as claimed every four weeks over a period of 24 weeks or longer without the emergence of tolerance or negative side effects. (Ex. 2055 ¶¶ 88–89.)

Though Comer's "Introduction" mentions that "[t]olerance does not develop . . . and [naltrexone] has few side effects, even after chronic administration of over 1 year" (*Id.* at 351), the underlying reference is directed to *oral* dosing "three times per week (in contrast to once every four weeks), i.e., 100 mg on Monday and Wednesday and 150 mg on Friday" (Ex. 2024 at 67.) Development of a satisfactory, parenterally administered, *long-acting* formulation was more difficult. (*See, e.g.*, Ex. 2023 at 5 (Park-authored article stressing "the difficulty associated with developing parenteral depot formulations," as opposed to oral formulations);

see also Ex. 2056 ¶ 30 (explaining formulation challenges specific to naltrexone).) Indeed, Comer acknowledged potential problems with depot naltrexone, such as the weeks-long indurations observed by Kranzler when using the same formulation. (Ex. 1010 at 359 (citing Ex. 1011).) Comer also notes the potential for “negative side-effects typically reported after naltrexone administration,” such as gastrointestinal complaints or effects on mood. (*Id.* at 359.)

b) Claims 7–9: The Asserted Combination Does Not Teach a Second Administration At Least About 7 Days After the First

Dependent claims 7–9 recite “a second administration of a long acting formulation comprising naltrexone.” (Ex. 1001 at 21:26–22:5.) In an attempt to satisfy this claim limitation, Amneal makes the nonsensical and unsupported assertion that “Comer and Nuwayser both teach four-week dosing, [and] a POSA would not consider a second dose earlier than seven days.”²⁴ (Pet. at 34–35 (citing to Ex. 1030 ¶ 111).)

First, none of the references cited by Amneal teach a second administration of a long-acting naltrexone formulation. (Ex. 2055 ¶¶ 57, 76, 85.) The claims should be confirmed for this reason alone because fewer than all claim features are disclosed in the prior art. (*See* § IV.B.2, *supra*.)

²⁴ Again, Dr. Park is not a medical doctor. (*See* § III.A.3.a n.12, *supra*.)

Second, the cited portion of Dr. Park’s testimony is conclusory and not keyed to objective proof regarding the understanding of a person of ordinary skill in the art. (*See, e.g.*, Ex. 1030 ¶ 111 (“I can see no reason why a POSA would consider using anything other than identical doses for successive doses. Anything else would be out of the ordinary.”).) Therefore, in accordance with 37 C.F.R. § 42.65(a), Dr. Park’s testimony should be given little or no weight.²⁵ *See Coal.*

²⁵ Dr. Park’s testimony has been frequently criticized by the PTAB and district courts. *See, e.g., Coal. For Affordable Drugs XI LLC v. Insys Pharma, Inc.*, IPR2015-01799, Paper 9 at 12 (Mar. 10, 2016) (“Dr. Park’s sweeping, but unsupported, opinion . . . is insufficient to support a successful anticipation challenge”); *Endo Pharms. Inc. v. Depomed, Inc.*, IPR2014-00656, Paper 66 at 32 (Sept. 21, 2015) (“we accorded Dr. Park’s test results little to no weight”); *Shire LLC v. Mylan Pharms., Inc.*, No. 11-55, 2013 U.S. Dist. LEXIS 5279 at *36 (N.D. W.Va. Jan. 14, 2013) (“[Dr. Park’s] affidavit on this issue merely recites Mylan’s theory without reference to any industry publications or other independent sources”); *Eisai v. Glenmark Pharms. Ltd.*, No. 13-1279, 2015 U.S. Dist. LEXIS 32462, *36–37 (D. Del. Mar. 17, 2015) (“[Dr. Park] unpersuasively characterizes the relevant entry in the *Handbook of Pharmaceutical Excipients*”); *Aventis* (Continued. . .)

For Affordable Drugs XI LLC v. Insys Pharma, Inc., IPR2015-01797, Paper 9 at 9 (Mar. 10, 2016) (criticizing Dr. Park for this very reason).

c) Claims 2 & 11: The Asserted Combination Does Not Exclude a Prior Oral Dose of Naltrexone

Dependent claims 2 and 11 recite methods of treatment that do not follow prior exposure to oral naltrexone. Specifically, claim 2 recites “not us[ing] oral naltrexone within five or more days before” the claimed administration of a long-acting formulation. (Ex. 1001 at 21:13–14.) For its part, claim 11 recites “not receiv[ing] an initial oral dose of naltrexone.” (*Id.* at 22: 8–9.) In its attempt to satisfy these claim limitations, Amneal points to (i) Comer’s mention of a possible “treatment setting where oral naltrexone may not be given prior to depot naltrexone” and (ii) Nuwayser’s lack of explicit disclosure that subjects received initial oral doses of naltrexone. (Pet. at 33–35.)

Regardless of Comer’s brief reference to a hypothetical “treatment” scenario (see § III.A.3, *supra* (explaining why Comer’s protocol does not constitute “treat[ment]”)), Amneal cannot contest the fact that Comer’s study participants received oral naltrexone two days before depot administration and thus fall outside the scope of claims 2 and 11 as properly construed. (See § II.C., *supra*; Ex. 1010

Pharma S.A. v. Hospira, 743 F. Supp. 2d 305, 344 n.8 (D. Del. 2010) (“Dr. Park seemed to blur [a claim construction] issue”).

at 353.) And if a POSA were to recognize “the sameness of the AUC plots of Comer and Nuwayser,” (Pet. at 31), then Amneal failed to explain why such sameness would not also apply to sameness of protocol—including prior exposure to oral naltrexone, as explicitly mentioned in Comer. The asserted combination does not teach treatment without an initial oral dose. Because fewer than all features of claims 2 and 11 were disclosed in the prior art, the asserted combination of references does not render them obvious. *See, e.g., K/S HIMPP*, 751 F.3d at 1366.

C. Ground 5: The Claims Are Not Obvious Over Nuwayser, Kranzler, Rubio, and Wright

Ground 5 relies on the same references as Grounds 3 and 4, but incorporates Kranzler (Ex. 1011) rather than Comer. The Board correctly found that Amneal has no reasonable likelihood of prevailing on this ground. (Paper 8 at 33.) As explained below, the combination of Nuwayser, Kranzler, Rubio, and Wright does not render obvious the contested claims.

1. The Asserted Combination Does Not Disclose a Single Injection of Naltrexone Within the Claimed Range of Doses

As previously discussed, Kranzler teaches away from injections comprising more than 206 mg naltrexone. (*See* § IV.C.3.) None of the other references in this combination disclose “the step of parenterally administering a long acting formulation comprising about 310 mg to about 480 mg of naltrexone.” Thus, the

asserted combination fails to meet this claim limitation for the same reasons discussed in Sections III.A.1., III.B.1., and IV.B.1.

2. The Asserted Combination Does Not Disclose the Claimed AUC Differential

For the claimed AUC differential, Amneal again points to Nuwayser. (Pet. at 39.) As discussed above, however, Nuwayser does not disclose AUC, let alone the claimed AUC differential.²⁶ (See § III.B.2., *supra*.) For that reason alone, Ground 5 must fail.

3. The Asserted Combination Does Not Disclose the Claimed Range of Doses

Rather than attempting to rely on Comer for disclosure of the claimed range of doses (i.e., “about 310 mg to about 480 mg of naltrexone”), Amneal conclusorily alleges that “[i]t would be obvious to determine the dose that resulted in the disclosed AUC [of Nuwayser] without undue experimentation by generating a standard curve. 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.” (Pet. at 40 (citing Ex. 1030 ¶ 116).)

²⁶ Amneal relies on Rubio (Ex. 1028) and Wright (Ex. 1018) with respect to other claim terms.

A POSA would not have understood Nuwayser to disclose AUC in the first place. (See § III.B.2., *supra.*). Even if Nuwayser did, Amneal’s reliance on routine experimentation to determine dose serves as a perfect example of why “reference to ‘routine testing’ or ‘routine experimentation’ is disfavored.” *Pfizer*, 480 F.3d at 1367. Of the cited testimony, the Board observed that “Dr. Park does not support [his] statements with any details about how [his] calculations would be performed, or provide any specific evidence supporting these statements.” (Paper 8 at 34.) Rather, Dr. Park plots hypothetical values on his standard curve at doses of 100 mg, 200 mg, 300 mg, and 400 mg naltrexone and then arbitrarily draws a line that provides the result that Amneal seeks.²⁷ This is hindsight. (Ex. 2055 ¶ 98 (explaining problems with Dr. Park’s hypothetical standard curve).)

Also flawed is Amneal’s argument that Kranzler “would provide at least a starting point” for dose. (Pet. at 33.) First, there is no basis for assuming that formulations providing plasma levels of 1 ng/mL necessarily brought about therapeutic effect. (See § III.A.3.a.) Second, Kranzler *teaches away* from using the claimed range of doses in a single injection. Indeed, Kranzler reports that 73% of its subjects suffered induration that lasted, on average, 2.8 weeks. (Ex. 1011

²⁷ Dr. Park’s reliance on hypothetical points highlights the reason why neither Comer nor Nuwayser nor Kranzler reported AUC.

at 1076.) Kranzler therefore suggests “*reducing* the total dose of [206 mg naltrexone] in each injection”—not increasing it to the claimed range of “about 310 mg to about 480 mg” in a single injection (*see* § II.B.1.)—in order to “reduce adverse effects.” (*See* Ex. 1011 at 1078.)

4. A POSA Would Not Have Been Motivated Or Had a Reasonable Expectation of Success in Combining the Asserted References

Amneal’s failures of proof regarding motivation to combine and reasonable expectation of success are reflected in its allegation that a POSA could have used Kranzler as a starting point to arrive at the claimed methods. (*See, e.g.*, Ex. 1030 ¶ 117.) Indeed, Kranzler makes no mention of Depotrex™ and focuses on the use of naltrexone in *alcohol*-dependent subjects. (Ex. 1011 at 1075.) While its results may “support . . . potential clinical utility” for that indication (*id.* at 1074), Kranzler excludes potential subjects ever diagnosed with opioid dependence (*id.* at 1075), such as Nuwayser’s “heroin addicts” (Ex. 1014 at 19:24.) To the extent that Nuwayser mentions countering the effects of alcohol, it turns to a different active ingredient: nalmefene. (*Id.* at 5:62–65.)

Also, as discussed above (*see* § IV.C.3., *supra*), Kranzler teaches away from injections comprising more than 206 mg naltrexone, since “reducing the total dose” might in turn “reduce adverse effects.” (Ex. 1011 at 1078.) Amneal has

failed to explain why a POSA might have ignored that directive and instead pursued formulations comprising “about 310 mg to about 480 mg.”

5. At a Minimum, Dependent Claims 2, 6–9, and 11 Are Not Obvious Over Nuwayser, Kranzler, Rubio and Wright

The substitution of Kranzler for Comer does not cure any deficiencies detailed in Sections IV.B.4., *supra*.

D. Ground 6: The Claims Are Not Obvious Over Alkermes 10-K, Vivitrex Specimen, Rubio, and Wright

Ground 6 boils down to unfounded speculation that a POSA would have: (i) accessed Alkermes’s 10-K (Ex. 1016) through the SEC’s archives; (ii) noticed the 10-K’s reference to “Vivitrex™”; (iii) searched for that mark in the USPTO’s trademark database; (iv) found the Vivitrex Specimen (Ex. 1017), which mentions “Medisorb®”; (v) turned to Wright (Ex. 1018) for methods of manufacturing microparticles; and then (iv) recognized “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.” (Pet. at 44–47.) The Board correctly found that Amneal has no reasonable likelihood of prevailing on this ground. (Paper 8 at 35.)

1. Neither the Alkermes 10-K nor the Vivitrex Specimen Qualify as Prior Art

a) The Alkermes 10-K

As the Board has already recognized (Paper 8 at 37), Amneal fails to establish that the Alkermes 10-K was catalogued or indexed in a way that might

establish public accessibility. *See In re Lister*, 583 F.3d 1307, 1312 (Fed. Cir. 2009). Nor does Amneal provide testimony that might support public accessibility of the 10-K. *See Liberty Mut. Ins. Co. v. Progressive Cas. Ins. Co.*, CBM2013-00009, Paper 68 at 18–19 (Feb. 11, 2014). Further, nothing in the record establishes that a POSA would have looked for the 10-K or known that it existed, let alone known how to access it. *See Celltrion, Inc. v. Biogen, Inc.*, IPR2017-01095, Paper 12 at 21 (Oct. 6, 2017).²⁸

b) The Vivitrex Specimen

According to Amneal, a Vivitrex trademark appeared in the Official Gazette in 2002 (Ex. 1020). (See Pet. at 44–45.) But the Official Gazette makes no mention of the asserted Vivitrex Specimen and does not disclose the particular amounts of naltrexone for which Amneal relies on the reference. (See, e.g., Pet. at 52, claim feature “1(c),” Ground 6.) Thus, Amneal turns to the Trademark Applications and Registrations Retrieval database. (Pet. at 45.) But the existence of such a database and its purported disclosure of “information regarding the status and prosecution history” of trademark applications does not establish that the Vivitrex Specimen was “sufficiently accessible to the public interested in the art” under *In re*

²⁸ Dr. Park admitted that none of his “research publication[s]” make “reference to a 10-K.” (Ex 2025 at 135:15–25.)

Klopfenstein, 380 F.3d 1345, 1351–52 (Fed. Cir. 2004). As the Board has noted (Paper 8 at 38), Dr. Park’s testimony on this point is expressly based on “understand[ing] from counsel”—highlighting a POSA’s lack of familiarity with these non-technical documents. (Ex. 1030 ¶ 130.)

2. A POSA Would Not Have Been Motivated Or Had a Reasonable Expectation of Success in Combining the Asserted References

As the Board recognized, the Petition fails to establish that a POSA “would have been motivated to combine the teachings of [the Alkermes 10-K] with Vivitrex Specimen, Rubio, and/or Wright.”²⁹ (Paper 8 at 38.) Ground 6 hinges on the unsupported proposition that the 10-K’s use of “Vivitrex™” “would lead a POSA to check whether or not there was a pending trademark registration at the time of the 10-K filing.” (Pet. at 45.) The Petition lacks support for any such motivation, and is instead “undermine[d]” by Dr. Park’s admission that he “understand[s] from counsel that USPTO records are public and that the trademark specimen for Vivitrex is part of the prior art.” (Paper 8 at 38 (quoting Ex. 1030 ¶ 130).)

²⁹ Nor does Amneal attempt to explain why a POSA would review non-technical investor documents like a 10-K in the first place.

3. The Asserted Combination Does Not Teach or Suggest All Claim Features

Ground 6 also must fail because the asserted combination does not teach the claimed AUC differential. (*See* § IV.B.2., *supra*, discussing *KSR* and *K/S HIMPP*.) Instead, Amneal posits that “It would be readily apparent to a POSA that at least one of [Wright’s] three particles was used in the study of the ’499 Patent and would result in the same AUC as identified in the ’499 Patent.” (Pet. at 47.) Yet that effort to conjure up the missing claim limitation is improper—it relies on the teachings of the ’499 patent itself with respect to a POSA’s understandings of AUC (and thus AUC differential) that is absent from the asserted combination. *See, e.g., Orthopedic*, 702 F.2d at 1012; see also *Dr. Reddy’s Labs., Inc. v. Pozen Inc.*, IPR2015-00802, Paper 28 at 26 (Oct. 9, 2015) (“reliance on the teachings of the [contested] patent is impermissible hindsight”).

The claimed AUC differential is “not expressly found” in the asserted combination. (*See, e.g.,* Pet. at 47.) Therefore Amneal attempts to rely on Wright as “explain[ing] how to make the Vivitrex formulation” (Pet. at 47) and on Dr. Park’s testimony that the AUC differential is an “inherent property of Vivitrex, or at the very least, . . . consequence[s] of its formulation” (Ex. 1030 ¶ 134). Perhaps contemplating the fact that Wright does not disclose the claimed range of doses (*see, e.g.,* Pet. at 52 (citing the Vivitrex Specimen, rather than Wright)), Dr. Park concedes that AUC differentials of Vivitrex and Wright may not be identical and

that some variation might exist. (See Ex. 1030 ¶ 134 (“A POSA would expect that their pharmacokinetic properties, such as AUC and AUC differential and their therapeutic efficacy, would be identical. . . . If not, any variation would be minor and well within a POSAs reasonable expectation.”).) In light of Dr. Park’s latter admission, variations might fall outside the scope of the contested claims, Dr. Park does not state that such variations would never result in an AUC or AUC differential that falls outside the scope of the contested claims, so Ground 6 must fail. The Federal Circuit has “emphasized that the limitation at issue *necessarily* must be present in order to be inherently disclosed.” *Southwire Co. v. Cerro Wire LLC*, 870 F.3d 1306, 1311 (Fed. Cir. 2017).

E. Objective Indicia Support a Finding of Nonobviousness

Objective indicia must be considered in determining whether a patent is obvious. *Apple Inc. v. ITC*, 725 F.3d 1356, 1365 (Fed. Cir. 2013). In fact, “secondary considerations may often be the most probative and cogent evidence [of nonobviousness] in the record.” *Star*, 655 F.3d at 1375 (internal quotation marks omitted). Even if “the first three *Graham* factors favor a determination that the challenged claims are obvious,” a “case for non-obviousness based on secondary considerations [that] is particularly strong [can] outweigh[] the other three factors.” *Intri-Plex Techs.*, IPR2014-00309, Paper No. 83 at 45–46. Here, patentability of the challenged claims is supported by secondary considerations of

nonobviousness, including commercial success of Vivitrol (the commercial embodiment of the challenged claims), failure of others, long-felt, but unmet need, unexpected results, industry skepticism, and industry recognition and praise.

1. Commercial success

“[T]here is a presumption of nexus³⁰ for objective considerations when the patentee shows that the asserted objective evidence is tied to a specific product and that product ‘is the invention disclosed and claimed in the patent,’” as is the case here. *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1329 (Fed. Cir. 2016). The contested claims in this case cover Alkermes’s highly successful Vivitrol medication (*e.g.*, Ex. 1001 at 2:29–36; *see also* Pet. at 49 (“the formulations of Vivitrex and those used in the ’499 patent are the same . . . the AUCs should be the

³⁰ Petitioner notes that there are 16 patents listed in the Orange Book for Vivitrol (Pet. at 60), but correctly does not assert that any of the other 15 are blocking patents. None of the other 15 patents prevent a POSA from developing their own formulation of naltrexone and indeed, numerous other naltrexone dosage forms have been approved, from as early as 2002. Moreover, the ’499 patent is the only patent in the Orange Book that does not expire by May 2020, and there are no unexpired regulatory exclusivities attached to Vivitrol that would prevent a POSA from now developing their own long acting injectable formulation of naltrexone.

same”); Ex. 2003), which in 2017 achieved about \$270 million in net sales—about a 33% increase from 2016. (Ex. 2021 at 56.)

The Federal Circuit has repeatedly found a nexus where evidence of secondary considerations pertains to benefits flowing from the claimed invention. *Demaco Corp. v. F. Von Langsdorff Licensing Ltd.*, 851 F.2d 1387, 1392 (Fed. Cir. 1988) (finding a nexus where “the thing (product or method) that is commercially successful is the invention disclosed and claimed in the patent.”) Further, “[t]he presumed nexus cannot be rebutted with mere argument; evidence must be put forth.” *Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 229 F.3d 1120, 1130 (Fed. Cir. 2000).

Here, there can be no doubt that Vivitrol’s strong sales flow from its increased efficacy and safety compared to the available approved products, which directly flow from the claimed features, particularly the AUC relative to prior art oral naltrexone. The AUC profile helps to ensure patient compliance—which has resulted in Vivitrol’s commercial success over prior oral naltrexone regimens. Indeed, the FDA has recognized that “[c]onsistent product performance over 28 days is pivotal for [Vivitrol’s] safety and efficacy.” (Ex. 2007 at Page 10 of 43.)

2. Others Failed and There Was a Long-Felt, But Unsolved, Need

“Evidence of long-felt need is particularly probative of obviousness when it demonstrates both that a demand existed for the patented invention, and that others

tried but failed to satisfy that demand.” *Millennium Pharm., Inc. v. Sandoz Inc.*, 862 F.3d 1356, 1368 (Fed. Cir. 2017) (reversing the district court’s finding of obviousness based, in part, on a finding of long-felt but unsolved need).

Tellingly, naltrexone injections were being tested as early as 1984. (Ex. 1025; Ex. 1012). Yet, by the early 2000s there were only a handful of depot formulations that had potential to become a clinically meaningful treatment. (See, e.g., Ex. 1001; Ex. 1010; Ex. 1011; Ex. 1015; Ex. 2056 ¶ 31–32.) Some of these experimental injectable formulations failed to produce a meaningful effect without significant adverse effects. (Ex. 1011 at 1076.) And a review of the literature, including the references cited by Amneal, fails to show an established dose³¹ capable of clinically treating a patient with an injectable naltrexone formulation (Ex. 2056 ¶ 31)—neither Biotek’s formulation (Ex. 1014) nor Southern Research Institutes’ formulation (Ex. 1015) nor DrugAbuse Sciences’ formulation (Ex. 1050 at 742) were ever commercially marketed. As late as 2003 it was reported that several attempted formulations failed to show clear evidence of clinical success due to “inconsistent initial and sustained release rates, . . . inadequate duration of

³¹ See Ex. 1010 (192 mg or 384 mg); Ex. 1011 (206 mg); Ex. 1012 (63 mg) Ex. 1013 (103 mg or 206 mg); Ex. 1015 (300 mg); Ex. 1019 (52 mg or 104 mg); Ex. 1025 (63 mg).

release, suboptimal physical characteristics (dose size/volume, naltrexone loading), and local site reactions.” (Ex. 2010 at 1979–80 (citations omitted); *see also, e.g.*, Ex. 1015 at 2:8–25 (noting the “constraints on a satisfactory slow-release injectable formulation” include making sure “the level of drug maintained in the subject must be at an effective level, without reaching any hazardous level” while also ensuring that “metabolites that are produced must be acceptable levels.”).)

Prior to the 2004 application that gave rise to the ’499 patent, there were no known solutions to the decades-old problems of patient compliance and fluctuating plasma concentrations known to be associated with oral naltrexone dosage forms. (Ex. 2010 at 1974; Ex. 2056 ¶¶ 16, 29.) Vivitrol was the first (and is still the only) naltrexone injection to solve these long-time problems and receive FDA approval. (Ex. 2056 ¶¶ 17, 33.) Following FDA approvals in 2006 and 2010, Vivitrol became the first and remains the only non-narcotic, non-addictive depot injection product FDA-approved for the treatment of alcohol dependence and for the prevention of relapse to opioid dependence, following opioid detoxification. (Ex. 2011 Page 2 of 19; Ex. 2003; Ex. 2056 ¶¶ 17, 33.)

3. The Claimed Invention Provided Unexpected Results

Unexpected results may be important objective evidence of nonobviousness. *See, e.g., Ortho-McNeil*, 520 F.3d at 1365. Indeed, “the inventor’s insights, willingness to confront and overcome obstacles, and yes, even serendipity, cannot

be discounted.” *Id.* at 1364. As discussed during the prosecution of the claims-at-issue (Ex. 1003 at 1; Ex. 1004 at 8), the claimed AUC profile was unexpected.

According to Amneal, Alkermes’s inventions are “inconsequential because [they] are not linked to any meaningful improvement in therapeutic efficacy” and because “any way of maintaining therapeutic blood levels of naltrexone of at least 1 ng/ml will be effective.” (Pet. at 2.) But Amneal’s cited references do not support that broad conclusion, nor could they, given Amneal’s use of vague terms like “meaningful improvement.” Dr. Park does nothing to clarify that term, and his testimony repeatedly confuses the concepts of (i) efficacy versus effectiveness and (ii) necessity versus sufficiency. For example, Dr. Park first states that “serum blood levels of at least 1 ng/ml[] . . . w[ere] recognized as necessary for efficacy” (Ex. 1030 ¶ 52) and later cites that reasoning to support his otherwise bare conclusion that “it was known that naltrexone provides effective treatment as long as its blood concentration is maintained at or above 1 ng/ml.” (*Id.* ¶ 60).

The contested claims “arose from the unexpected discovery that substantially improved serum levels of naltrexone can be achieved” by administering Vivitrol. (Ex. 1001 at 2:30–33; Ex. 1009 at Page 3; Ex. 2007 at Pages 22–23 of 43.) These data supported Alkermes’s claim of “increased efficacy and safety compared to the available approved products to treat alcohol dependence,” prompting the FDA to grant the application priority review.

(Ex. 2016 at 1.) Priority review signifies that Vivitrol, which embodies the claims, is a “*significant improvement* in the safety or effectiveness of the treatment . . . of a serious condition.” (Ex. 2046 at 24 (emphasis in original).) Such “significant improvement” includes “[d]ocumented enhancement of patient compliance.” (*Id.* at 24–25.)

4. There Was Skepticism in the Industry

The Federal Circuit has explained that “[g]eneral skepticism of those in the art . . . is . . . relevant and persuasive evidence of nonobviousness.” *Monarch Knitting Mach. Corp. v. Sulzer Moral GmbH*, 139 F.3d 877, 885 (Fed. Cir. 1998) (internal quotation marks omitted). And teaching away is a particularly “pointed and probative” type of skepticism. *Id.* at 885. As previously discussed, Kranzler teaches away from “the step of parenterally administering a long acting formulation” of naltrexone within the claimed range of doses (i.e., “about 310 mg to about 480 mg”), as properly construed to refer to “a single injection of a long acting formulation comprising about 310 mg to about 480 mg of naltrexone.” (See § II.A, *supra*.)

For instance, Kranzler discloses significant adverse effects, describing the tested naltrexone depot formulation as “not ideal” and calling for “[a]dditional study.” (Ex. 1011 at 1078.) It also suggests reducing the dose of naltrexone per injection (see § IV.C.3., *supra*)—which was already below the range of doses

claimed in the '499 patent (*see* § II.A., *supra*)—despite the fact that doing so would require “more frequent injections.” (Ex. 1011 at 1078.)

In addition, provided that patient compliance was considered to be one of the main shortcomings of oral naltrexone (Ex. 1010 at 351), side effects that would result in patient discomfort would discourage individuals returning for subsequent administrations. (Ex. 2056 ¶ 34; *e.g.*, Ex. 2040 at 123 (noting that “individualized medication dosages are probably the most important factor in patient retention . . . because they contribute to patient comfort”).) Likewise, the fact that the formulation studied in Comer required administrations to both buttocks (Ex. 1010 at 354) would result in less comfort compared to a “single gluteal injection.” (Ex. 2003 at 1; Ex. 2049 at 3 (suggesting to “[a]lternate the injection site each time you inject to avoid soreness at any one si[te].”).)

There was also skepticism as evidenced by the concerns that a sustained-release formulation of naltrexone may increase the use of non-opioid drug use, as well as concerns regarding adverse tissue reactions. (Ex. 2056 ¶ 36; Ex. 2041 at 9.) In addition, there was a general concern in the field that an addict should not be prescribed drugs as a means to address their addiction problems. (Ex. 2056 ¶ 24; Ex. 2009 at 2 (“healthcare providers, and patients themselves, sometimes question the value of using any drug to treat drug or alcohol addiction”).)

5. Vivitrol® Has Received Industry Praise and Recognition

Industry praise provides “probative and cogent evidence” of nonobviousness. *Institut*, 738 F.3d at 1347 . For Vivitrol, endorsement from fellow industry players was evident even prior to FDA approval. For example, Cephalon Inc. “agreed to pay as much as \$490 million to Alkermes Inc. for the development and U.S. commercial rights to [Vivitrol],” and Cephalon’s Chief Executive praised Vivitrol for addressing a “large and underserved” market. (Ex. 2051.) At the time of that agreement, Vivitrol was reported as merely “an experimental treatment for alcohol dependence.” (*Id.*)

Consistent with its commercial success, Vivitrol has also received significant industry acclaim for its “significant advancement in addiction treatment.” (Ex. 2037 (quoting Janet Woodcock, M.D., director of FDA’s Center for Drug Evaluation and Research).) For example, Dr. Stephen Markus of Creekside Center for Integrative Medicine was quoted stating that “Vivitrol is the most amazing medication that’s come on the market for opiate addiction.” (Ex. 2052.) Further, a New England Journal of Medicine (“NEJM”) article titled, *Extended-Release Naltrexone to Prevent Opioid Release Relapse in Criminal Justice Offenders*, received second place at the 2017 Top Ten Clinical Research Achievement Awards Ceremony at the National Press Club. (Ex. 2053; Ex. 2056 ¶¶ 10, 41.) This article in praising that “[e]xtended-release naltrexone . . . is

effective for the prevention of relapse to opioid dependence” used Vivitrol.

(Ex. 2043 at 1232.)

“The Top Ten Clinical Research Achievement Awards recognize major research advances that involve both innovation and impact on human diseases.” (Ex. 2053.) The NEJM study also received the Distinguished Clinical Research Excellence Award. (*Id.*) Likewise, in a recent summit hosted by the National Academies of Sciences, Engineering, and Medicine, Dr. Adam Bisaga, from Columbia University and the New York State Psychiatric Institute referred to XR-naltrexone³² “as an element of the comprehensive medical response to the opioid epidemic” and noted that, unlike methadone and buprenorphine, XR-naltrexone has no misuse or overdose risk. (Ex. 2039 at 1, 24; Ex. 2056 ¶¶ 24, 40.)

V. Conclusion

The Board should confirm the claims for various independent reasons explained in detail above. Among other fatal flaws, Grounds 1 and 2 lack disclosure of key claim limitations. Grounds 3–6 suffer from the same deficiency

³² Dr. Bisaga’s presentation focused on “FDA-approved medication for opioid-use dependence.” (Ex. 2039 at 2.) The only FDA approved extended-release medication for opioid use dependence is Vivitrol. (Ex. 2011 at 2; Ex. 2003; Ex. 2056 ¶ 40 n.2.)

and are further tainted by hindsight, as well as failures of proof with respect to motivation to combine and reasonable expectation of success. In addition, Ground 6 is built upon references that do not qualify as printed publications. Finally, various objective indicia favor a finding of nonobviousness. For at least these reasons, Amneal has not carried its burden with respect to Grounds 1–6, and the claims should be confirmed.

Respectfully submitted,

Dated: February 7, 2019

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Certificate of Compliance

Pursuant to 37 C.F.R. § 42.24(b)(1), the undersigned certifies that the foregoing Patent Owner's Response to Petition for *Inter Partes* Review of U.S. Patent No. 7,919,499 contains, as measured by the word-processing system used to prepare this paper, 13,868 words. This word count does not include the Table of Contents, Table of Authorities, List of Exhibits, Certificate of Compliance, or Certificate of Service. *See* 37 C.F.R. § 42.24.

Respectfully submitted,

Dated: February 7, 2019

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6(e), I certify that I caused to be served on the counsel for Petitioner a true and correct copy of the foregoing Patent Owner's Response to Petition for Inter Partes Review of U.S. Patent No. 7,919,499 by electronic means on February 7, 2019, at the following address of record:

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