APPENDIX A

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

NALPROPION PHARMACEUTICALS, INC.,
Plaintiff-Appellee

v.

ACTAVIS LABORATORIES FL, INC.,
Defendant-Appellant

2018-1221

Appeal from the United States District Court for the District of Delaware in No. 1:15-cv-00451-RGA, Judge Richard G. Andrews.

Decided: August 15, 2019

DOMINICK A. CONDE, Venerable LLP, New York, NY argued for plaintiff-appellee. Also represented by CHRISTOPHER P. BORELLO, JOSHUA DANIEL CALABRO, ZACHARY GARRETT, BRENDAN M. O'MALLEY.

JONATHAN D. BALL, Greenberg Traurig LLP, New York, NY, argued for defendant-appellant. Also represented by SCOTT JOSEPH BORNSTEIN, JUSTIN ALBANO MACLEAN, RICHARD CHARLES PETTUS.

Before PROST, *Chief Judge,* LOURIE and WALLACH, *Circuit Judges.*

Opinion for the court filed by *Circuit Judge* LOURIE.

Opinion dissenting in part filed by *Chief Judge* PROST.

LOURIE, Circuit Judge.

Actavis Laboratories FL, Inc. ("Actavis") appeals from the judgment of the U.S. District Court for the District of Delaware that (1) its proposed naltrexone hydrochloride and bupropion hydrochloride extended-release tablets, which are the subject of Abbreviated New Drug Application No. 208043 (the "ANDA product"), would infringe claim 1 of U.S. Patent 7,375,111 ("the '111 patent"), claims 26 and 31 of U.S. Patent 7,462,626 ("the '626 patent"), and claim 11 of U.S. Patent 8,916,195 ("the '195 patent"); (2) the asserted claims are not invalid; (3) the effective date of any FDA approval of ANDA No. 208043 shall be no earlier than the latest expiration of the '111, '626, and '195 patents; and (4) Actavis is permanently enjoined from manufacturing, using, or selling its ANDA product before the expiration of the patents in suit. *Orexigen Therapeutics, Inc. v. Actavis Labs. FL, Inc.,* 282 F. Supp. 3d 793 (D. Del. 2017) ("*Decision*"); Final Judgment, *Orexigen Therapeutics, Inc. v. Actavis Labs. FL, Inc.,* No. 1:15-cv-451 (D. Del. Oct. 26, 2017), ECF No. 186. Because we conclude that the district court did not err in finding claim 11 of the '195 patent not invalid for lack of written description, but did err in finding that claim 1 of the '111 patent and claims 26 and 31 of the '626 patent would not have been obvious in view of the prior art, we affirm-in-part and reverse-in-part.

BACKGROUND

Appellee Nalpropion Pharmaceuticals, Inc. ("Nalpropion")[1] holds New Drug Application No. 200063 for and markets Contrave® for weight management in overweight or obese adults. Relevant here are the three Orange Book-listed patents for Contrave® that Nalpropion asserted against Actavis: the '626, '195, and '111 patents.

The '626 patent is drawn to a method for treating overweight or obesity comprising (1) diagnosing an individual as suffering from overweight or obesity by body mass index, (2) administering bupropion in an amount effective to induce weight loss, and (3) administering naltrexone in an amount effective to enhance the weight loss activity of bupropion. '626

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[1] Takeda Pharmaceutical Company Limited ("Takeda Ltd."), Takeda Pharmaceuticals International GmbH, Takeda Pharmaceuticals USA, Inc. ("Takeda USA"), and Takeda Pharmaceuticals, America, Inc. (collectively, "Takeda") and Orexigen Therapeutics, Inc. ("Orexigen") filed this suit in the District of Delaware. At the time of filing, Orexigen owned all three patents in suit, Takeda Ltd. was the exclusive licensee of the patents, and Takeda USA held approved New Drug Application No. 200063 for extended-release tablets containing 8 mg of naltrexone hydrochloride and 90 mg of bupropion hydrochloride. During the litigation, Orexigen acquired all of Takeda's rights to Contrave®, including ownership of the NDA. Stipulation and Order at 1, *Orexigen Therapeutics, Inc. v. Actavis Labs. FL, Inc.,* No. 1:15-cv-451 (D. Del. Oct. 5, 2017), ECF No. 92. After this appeal was taken, however, Orexigen commenced bankruptcy proceedings under Chapter 11 of Title of the United States Code in the U.S. Bankruptcy Court for the District of Delaware and transferred ownership of the patents-in-suit to Nalpropion. Unopposed Motion for Substitution of Nalpropion Pharms. Inc. for Orexigen Therapeutics, Inc. at 1, *Nalpropion Pharm. Inc. v. Actavis Labs. FL, Inc.,* No. 18-1221 (Fed. Cir. Aug. 28, 2018), ECF No. 30.

patent col. 38 l. 60-col. 39 l. 4. Nalpropion asserted claims 26 and 31. Claim 26 depends from claim 25, which recites:

> A method of treating overweight or obesity, comprising administering a weight loss effective amount of a first and second compound to an individual who has been diagnosed as suffering from overweight or obesity in order to treat said overweight or obesity, wherein said first compound is bupropion, or a pharmaceutically acceptable salt thereof, and said second compound is naltrexone, or a pharmaceutically acceptable salt thereof, and wherein the weight loss activity of said first and second compounds is enhanced compared to the administration of the same amount of either compound alone.

Id. col. 40 ll. 16-26. Claim 26 adds the additional limitation that naltrexone and bupropion "are administered together." *Id.* col. 40. ll. 27-30. Claim 30 depends from claim 25 and requires that at least one of the drugs be in a "sustained-release formulation," *id.* col. 40 ll. 41-44, while claim 31, which depends from claim 30, requires that the drugs be "administered in a single oral dosage form," *id.* col. 40 ll. 45-49.

The '195 patent is also directed to methods of treating overweight or obesity, but the claims are drawn to specific dosages of sustained-release naltrexone and bupropion that achieve a specific dissolution profile. At issue here is claim 11:

> A method of treating overweight or obesity having reduced adverse effects comprising orally administering daily about 32 mg of

> naltrexone and about 360 mg of bupropion, or pharmaceutically acceptable salts thereof, to a person in need thereof, wherein the bupropion or pharmaceutically acceptable salt thereof is administered as a sustained release formulation, wherein the naltrexone or pharmaceutically acceptable salt thereof is administered as a sustained release formulation, and wherein said sustained release formulation of naltrexone has an in vitro naltrexone dissolution profile in a dissolution test of USP Apparatus 2 Paddle Method at 100 rpm in a dissolution medium of water at 37° C. of:
>
> a) between 39% and 70% of naltrexone released in one hour;
>
> b) between 62% and 90% of naltrexone released in two hours; and
>
> c) at least 99% in 8 hours;
>
> wherein about 16 mg of said sustained release formulation of naltrexone or a pharmaceutically acceptable salt thereof is administered twice daily, and about 180 mg of said sustained release formulation of bupropion or a pharmaceutically acceptable salt thereof is administered twice daily.

'195 patent col. 31 l. 5-col. 32 l. 3.

Finally, the '111 patent is directed to a composition of sustained-release bupropion and naltrexone for affecting weight loss. Asserted here is claim 1:

A composition for affecting weight loss comprising:

> (a) a sustained release formulation of bupropion or a pharmaceutically acceptable salt thereof in an amount effective to induce weight loss in an individual; and
>
> (b) a sustained release formulation of naltrexone or a pharmaceutically acceptable salt thereof in an amount effective to enhance the weight loss effect of the bupropion or salt thereof;
>
> wherein said composition is in a single oral dosage form fixed combination.

'111 patent col. 41 ll. 26-35.

Actavis filed an ANDA seeking to enter the market with a generic version of Contrave® prior to the expiration of the patents in suit, and Nalpropion responded by bringing an action for patent infringement, alleging that Actavis's ANDA product would infringe the '111, '626, and '195 patents. Actavis in turn brought invalidity counterclaims, challenging claim 11 of the '195 patent as invalid for lack of adequate written description and challenging claim 1 of the '111 patent and claims 26 and 31 of the '626 patents as invalid as obvious. The district court held a bench trial on all of these issues and held each claim not invalid and infringed. *Decision,* 282 F. Supp. 3d at 797.

First, the district court considered Actavis's written description argument. Actavis argued that claim 11 of the '195 patent lacked adequate written description support because its claimed dissolution profile was achieved using the USP Apparatus 2 Paddle Method ("USP 2"), but the specification discloses data obtained using the different USP Apparatus 1 Basket

Method ("USP 1"). The court was not persuaded that the use of a different method from what is prescribed in the claim presented a written description problem, holding that "whether the dissolution data reported in the specification was obtained using the basket method or the paddle method is not relevant to whether the inventors had possession of the invention." *Id.* at 802. Instead, the court credited Nalpropion's expert who opined that a person of ordinary skill would recognize that the inventors possessed an embodiment of the invention as described in Table 10, regardless whether USP 2 or a "'substantially equivalent' method" was used. *Id.* at 801 (citation omitted).

Next, the district court addressed the question of obviousness of claim 1 of the '111 patent and claims 26 and 31 of the '626 patent. Actavis argued that it would have been obvious for a person of skill to combine bupropion and naltrexone for treating overweight and obesity because both drugs were known to cause weight loss, but the court disagreed, finding Actavis's argument to be "a classic case of hindsight bias." *Id.* at 809.

Actavis appealed from the district court judgment, and we have jurisdiction under 28 U.S.C. § 1295(a)(1).

DISCUSSION

On appeal from a bench trial, we review a district court's conclusions of law *de novo* and its findings of fact for clear error. *Braintree Labs., Inc. v. Novel Labs., Inc.,* 749 F.3d 1349, 1358 (Fed. Cir. 2014). "A factual finding is clearly erroneous when, despite some supporting evidence, we are left with a definite and firm conviction that the district court was in error." *Alcon Research Ltd. v. Barr Labs., Inc.,* 745 F.3d

1180, 1186 (Fed. Cir. 2014) (citing *Alza Corp. v. Mylan Labs., Inc.,* 464 F.3d 1286, 1289 (Fed. Cir. 2006)). "The burden of overcoming the district court's factual findings is, as it should be, a heavy one." *Polaroid Corp. v. Eastman Kodak Co.,* 789 F.2d 1556, 1559 (Fed. Cir. 1986). "Where there are two permissible views of the evidence, the factfinder's choice between them cannot be clearly erroneous." *Anderson v. City of Bessemer City,* 470 U.S. 564, 574 (1985) (citing *United States v. Yellow Cab Co.,* 338 U.S. 338, 342 (1949)).

Whether a claim satisfies the written description requirement is a question of fact, *Ariad Pharm., Inc. v. Eli Lilly & Co.,* 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc), that we review for clear error, *Alcon,* 745 F.3d at 1190. "Whether an invention would have been obvious at the time it was made is a question of law, which we review de novo, based on underlying facts, which we review for clear error." *Tokai Corp. v. Easton Enters., Inc.,* 632 F.3d 1358, 1366 (Fed. Cir. 2011) (citing *Media Techs. Licensing, LLC v. Upper Deck Co.,* 596 F.3d 1334, 1337 (Fed. Cir. 2010)).

The district court rejected Actavis's invalidity arguments that (1) claim 11 of the '195 patent is invalid for lack of adequate written description and (2) claim 1 of the '111 patent and claims 26 and 31 of the '626 patent are invalid as obvious. We address the court's holdings in turn.

I. Written Description

Claim 11 of the '195 patent recites a method of treating overweight or obesity comprising orally administering about 16 mg of naltrexone and about 180 mg of bupropion, both in sustained-release formulations

administered twice daily. This method claim also requires that the claimed naltrexone formulation have an in vitro dissolution profile

> in a dissolution test of USP Apparatus 2 Paddle Method at 100 rpm in a dissolution medium of water at 37°C. of:
>
> a) between 39% and 70% of naltrexone released in one hour;
>
> b) between 62% and 90% of naltrexone released in two hours; and
>
> c) at least 99% in 8 hours . . . .

'195 patent col. 31 l. 14-col. 32 l. 3.

Example 1 of the specification discloses formulations of sustained-release naltrexone with varying amounts of either hydroxypropylmethyl cellulose (HPMC) or polyethylene oxide as excipients. The HPMC formulations range from 5% HPMC to 66% HPMC, and dissolution of these formulations was tested in Example 2 using 10-mesh baskets at 100 rpm. The 15% HPMC tablet released 39% of its naltrexone at one hour and 62% at two hours. *Id.* col. 17-18 (Table 5).

The first example in the specification to discuss a naltrexone-bupropion combination is Example 3, which describes tri-layer tablets with sustained-release naltrexone and bupropion layers on opposite sides of an inert layer. That formulation includes 10% HPMC. Dissolution of naltrexone was measured and reported in Table 10, but the specification is silent as to whether the data were obtained using USP 1 or USP 2. *Id.* at col. 20 ll. 1-11.

In finding adequate written description support for the claimed dissolution profile, the district court found that the values in Table 10—67% release in one hour and 85% release in two—fell squarely within the claimed range in claim 11. *Decision,* 282 F. Supp. 3d at 802. The court found the lower bounds were supported by the dissolution data for the 15% HPMC formulation in Table 5. *Id.*

Actavis had argued that neither table provided adequate written description support because the data listed were obtained using USP 1, but the court held that the dissolution technique used was not relevant because a person of skill would understand in the context of the patent that the inventors possessed the claimed invention. The court relied on Nalpropion's expert's testimony that a person of skill would understand that the inventors possessed the invention—whether USP 2 or a substantially equivalent method was used to measure it.

On appeal, Actavis repeats its argument that Tables 5 and 10 fail to provide adequate written description support for the claimed dissolution profile because the data in those tables were obtained using USP 1. According to Actavis, both inventor and expert testimony demonstrated that the two dissolution methods would produce different results. Actavis further argues that the data in Table 5 cannot support the claimed range because a person of ordinary skill in the art would not appreciate that the 15% HPMC data were relevant to the claims.

Nalpropion responds that there was no evidence that the data in either table were obtained using USP 1. Even if USP 1 had been used, however, Nalpropion

submits that a person of skill would understand the inventors to have had possession of their invention "irrespective of whether they used USP 1 or USP 2 because those methods are 'substantially equivalent.'" Appellee's Br. 22 (citing J.A. *Decision,* 282 F. Supp. 3d at 801-02). We conclude that the district court did not clearly err in finding that the inventors had possession of the invention consisting of treating overweight and obesity with the stated amounts of bupropion.

It is important to take note of the peculiarity of claim 11, which begins clearly enough by reciting a method of treating overweight or obesity by carrying out the specific, positive steps of administering a formulation of specific amounts of sustained-release naltrexone and bupropion in twice a day. The claim then records the dissolution data resulting from that formulation.

But that dissolution profile for naltrexone as measured by USP 2 relates only to the measurement of resultant in vitro parameters, not to the operative steps to treat overweight or obesity. And the district court concluded, on the facts, that USP 1 and USP 2 would be "substantially equivalent," *Decision,* 282 F. Supp. 3d at 801 (citation omitted). Thus, it found that, irrespective of the method of measurement used, the specification shows that the inventors possessed the invention of treating overweight or obesity with naltrexone and bupropion in particular amounts and adequately described it. We conclude that this finding does not present clear error.

As we explained in *Ariad,* the written description of an invention "must 'clearly allow persons of ordinary skill in the art to recognize that [the inventor]

invented what is claimed.'" 598 F.3d at 1351 (alteration in original) (quoting *Vas-Cath Inc. v. Mahurkar,* 935 F.2d 1555, 1563 (Fed. Cir. 1991) (Rich, J.) (citing *In re Gosteli,* 872 F.2d 1008, 1012 (Fed. Cir. 1989))). "In other words, the test for sufficiency is whether the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession *of the claimed subject matter* as of the filing date." *Id.* (emphasis added). It is not necessary that the exact terms of a claim be used *in haec verba* in the specification, and equivalent language may be sufficient.

To support their respective positions, both parties point to evidence regarding whether a person of skill would understand USP 1 and USP 2 to be "substantially equivalent." But the court credited Nalpropion's expert, Dr. Treacy, as more credible over what it interpreted as untrustworthy, self-serving statements by Actavis's expert, Dr. Mayersohn. *See Decision,* 282 F. Supp. 3d at 801-02 ("It seems to me that Dr. Mayersohn's theoretical opinion that the methods would yield different results is at odds with his reliance on a prior art reference using the basket method to argue that claim 11, which specifies the paddle method, was obvious."). The district court performed precisely its fact-finding function, weighing credibility of testimony. *See* Fed. R. Civ. P. 52(a)(6) ("Findings of fact, whether based on oral or other evidence, must not be set aside unless clearly erroneous, and the reviewing court must give due regard to the trial court's opportunity to judge the witnesses' credibility."). We do not disturb this finding.

Having found USP 1 and USP 2 substantially equivalent, the district court found Table 5 and Table 10

adequately supported the dissolution data ranges in claim 11. Particularly, the court was not convinced that relying on data from two tables presented a written description issue, noting that it found "nothing odd or invalidating about the inventors looking to different tables of dissolution data and other places in the specification to determine the ranges for the claimed dissolution profile," and finding that "multiple tests are necessarily required to establish a range." *Decision,* 282 F. Supp. 3d at 803. The court relied on the 15% HPMC data in Table 5, crediting both expert's testimony that 15% HPMC formulations were the first listed in the table in which a person of skill in the art would observe "a sustained release profile." *Id.* at 802 (quoting J.A. 11369:6-19, 11409:10-17). The court also credited Dr. Treacy's testimony that the 99% dissolution at eight-hour data point was supported by Table 10's disclosure, discounting Dr. Mayersohn's view that the dissolution profile would plateau and never reach the claimed 99% at eight hours. *Id*. While Actavis may disagree with the court's findings, these findings are supported by the record, and we do not disturb them. *See Anderson,* 470 U.S. at 573-74 ("If the district court's account of the evidence is plausible in light of the record viewed in its entirety, the court of appeals may not reverse it even though convinced that had it been sitting as the trier of fact, it would have weighed the evidence differently.").

The district court was convinced by its fact findings that Actavis had not proven by clear and convincing evidence that claim 11 of the '195 patent is invalid for lack of adequate written description. While as a general matter written description may not be satisfied

by so-called equivalent disclosure, in this case, buttressed by the district court's fact-finding, and where the so-called equivalence relates only to resultant dissolution parameters rather than operative claim steps, we affirm the district court's conclusion. Rigidity should yield to flexible, sensible interpretation.

II. Obviousness

Actavis also challenges claim 1 of the '111 patent and claims 26 and 31 of the '626 patent as obvious in view of O'Malley and Jain. We begin by reviewing the relevant references.

O'Malley is U.S. Patent 6,541,478, entitled "Smoking Cessation Treatments Using Naltrexone and Related Compounds." J.A. 7912. O'Malley teaches that weight gain is "[t]he significant problem" with smoking cessation and discloses use of opioid antagonists, including naltrexone, alone or with other withdrawal attenuating agents to minimize weight gain during treatment. O'Malley col. 1 l. 59-62. Claim 1 of O'Malley is drawn to a method of treating a person for nicotine dependency and minimizing weight gain during smoking cessation therapy comprising "administering . . . an effective amount of naltrexone and another compound selected from the group consisting of . . . bupropion. . . ." *Id.* col. 12 ll. 30-37.

Jain[2] is a research paper entitled "Bupropion SR vs. Placebo for Weight Loss in Obese Patients with Depressive Symptoms." J.A. 7171. Jain notes that "[p]reliminary studies suggest that bupropion SR is

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[2] desh K. Jain et al., Bupropion SR vs. Placebo for Weight Loss in Obese Patients with Depressive Symptoms, 10 OBESITY RES. 1049-56 (2002), J.A. 7171-78 ("Jain").

also an effective adjunct to diet for weight loss during acute and long-term therapy in nondepressed patients" and "is associated with weight loss in overweight or obese depressed patients." J.A. 7171. The authors then describe their double-blind study where sustained-release bupropion was administered in conjunction with a 500-kcal deficit diet. Sustained-release bupropion was found to be more effective than placebo at reducing weight in obese patients with depressive symptoms.

Additional references provide context for the obviousness arguments in this case: (1) Anderson for bupropion, (2) Atkinson and Bernstein for naltrexone, and (3) Dante for both naltrexone and its combination with bupropion.

Anderson[3] discloses a 48-week double-blind, placebo-controlled trial where sustained-release bupropion was administered to obese adults. J.A. 7160. Adjusted for placebo, subjects lost 2.2% and 5.5% of net bodyweight with 300 mg/d and 400 mg/d of sustained-release bupropion, respectively. *Id.*

Atkinson[4] examined the effects of long-term naltrexone administration on body weight and obesity, administering naltrexone to 60 obese subjects over 8 weeks. J.A. 8948. Atkinson found a small but significant weight loss in women but no significant effect in

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[3] James Anderson et al., *Bupropion SR Enhances Weight Loss: A 48-Week Double-Blind, Placebo-Controlled Trial,* 10 OBESITY RES. 633-41 (2002), J.A. 7160-68 ("Anderson").

[4] Richard Atkinson et al., *Effects of Long-Term Therapy with Naltrexone on Body Weight in Obesity,* 38 CLIN. PHARMACOL. THER. 419-22 (1985), J.A. 8948-51 ("Atkinson").

men. Similarly, Bernstein[5] teaches a method for curbing carbohydrate cravings and overeating through long-term administration of low-dose naltrexone. Bernstein comments that the administration of naltrexone as described "would benefit . . . obese persons." J.A. 7181 ¶ 13.

Dante, U.S. Patent 5,817,665, teaches use of an opioid antagonist like naltrexone with serotonin or norepinephrine reuptake inhibitors to treat mental and emotional disorders. Of note are Examples 2 and 3. Example 2 describes a woman in her thirties who was started on naltrexone without making any other changes. Dante col. 6 ll. 16-17. She rapidly lost her craving for sweets and lost thirty pounds in three weeks. *Id*. col. 6. l. 18-19. Example 3 describes similar results in an obese man. *Id.* col. 6. ll. 32-56. While these examples address only administration of naltrexone, the claims in Dante focus on its combination with bupropion. Claim 1 of Dante is drawn to "[a] method of treating depression comprising administering to a patient a pharmacologically effective dose of an opioid antagonist" and a "nontricyclic antidepressant[]." *Id.* col. 8 ll. 19-30. Claim 7 requires that the "nontricyclic antidepressant" be "selected from a group" including bupropion. *Id.* col. 8. ll. 47-51.

Despite these references, the district court rejected Actavis's obviousness argument. According to the district court, the weight loss effects of bupropion were known to be relatively modest at best, and prior art references reported potential risks, including a potential for seizures. Because a person of skill would not

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[5] U.S. Patent Application 2002/0198227, J.A. 7179-85 ("Bernstein").

understand bupropion's mechanism of action and because of its modest effectiveness, the court concluded that a person of skill would not have found bupropion to be an obvious starting point for further study. *Decision,* 282 F. Supp. 3d at 807.

The district court was also convinced that a person of skill would not have understood naltrexone to be effective for weight loss. The court did not find Bernstein to disclose weight loss and read Atkinson's disclosure of weight loss in women to be counterbalanced by increased body weight in men. *Id.* at 808.

As for the combination of the two drugs, the district court concluded that Dante and O'Malley did not teach a person of ordinary skill that the combination was effective for weight loss. *Id.* at 809. According to the court, neither reference teaches anything about weight loss or that naltrexone enhances bupropion's weight loss effects. The court likewise discounted the disclosure in Jain because men experienced weight gain. *Id.*

Finally, persuaded that the synergistic effect of the combination was an unexpected result and that others had failed to develop safe and effective weight loss drugs, the district court held that secondary considerations supported a finding of nonobviousness. *Id.* at 810.

On appeal, the parties primarily dispute whether a person of skill would have been motivated to combine bupropion, as disclosed by Jain, and naltrexone, as disclosed in O'Malley, to arrive at the claimed composition of the '111 patent and the method of the '626 patent with a reasonable expectation of success. Actavis argues that the district court incorrectly

interpreted the prior art and discounted the fact that both compounds were known to affect weight loss and had been administered together for that purpose. Appellant's Br. 56. In response, Nalpropion submits that naltrexone was not known to affect weight loss, bupropion had safety concerns and yielded only modest weight loss, and the combination had been used only to treat depression or to minimize weight gain in smoking cessation therapy. Nalpropion also argues that naltrexone was not known to enhance bupropion's effectiveness for weight loss.

Obviousness is a question of law, supported by underlying fact questions. *In re Baxter Int'l, Inc.* 678 F.3d 1357, 1361 (Fed. Cir. 2012). In evaluating obviousness, we consider the scope and content of the prior art, differences between the prior art and the claims at issue, the level of ordinary skill in the pertinent art, and any secondary considerations. *Graham v. John Deere Co. of Kan. City,* 383 U.S. 1, 17-18 (1966); *see also Apple Inc. v. Samsung Elecs. Co.,* 839 F.3d 1034, 1048 (Fed. Cir. 2016) (en banc) ("Objective indicia of nonobviousness must be considered in every case where present.").

We agree with Actavis and conclude that the claims at issue would have been obvious to a person of skill in the art in view of O'Malley and Jain. The prior art here discloses the claimed components of the composition claims and the steps of the method claims including the use claimed by the method.

The references teach that bupropion causes weight loss. For example, Jain specifically teaches that sustained-release bupropion was "an effective adjunct to diet for weight loss" in both non-depressed and

depressed patients, J.A. 7171, and was well-tolerated, J.A. 7177. This statement is confirmed by Anderson, which discloses the results from a 48-week, double-blind, placebo-controlled trial. J.A. 7160. Notably, Anderson's data indicate that administration of sustained-release bupropion yielded weight loss in non-depressed patients. J.A. 7161, 7165. Anderson's reported weight loss was dependent on bupropion SR dosage. J.A. 7165. Even Dr. Weber, a named inventor of the '626 and '111 patents, confirmed that bupropion had been considered safe and had weight loss effects. J.A. 11028-29.

Likewise, the record indicates that naltrexone can cause weight loss. Atkinson reports statistically significant weight loss in female obese patients and states that "naltrexone or similar drugs may have a role in the clinical treatment of obesity." J.A. 8950. While Atkinson reports weight loss only in women, the claims are not limited to men, and Dante discloses weight loss in two examples—for both a man and a woman. In Example 2, an obese woman was started on 25 mg of naltrexone and rapidly "lost her craving for sweets and a weight loss effort which was stalled took off. She lost thirty pounds in three weeks." Dante col. 6 ll. 16-19. Similarly, 25-50 mg of naltrexone was administered to an obese man in Example 3, and he reported losing about 10 pounds a week and no longer craved sweets. *Id.* col. 6 ll. 32-51. Bernstein also discloses that naltrexone reduces carbohydrate cravings and administration of it would benefit "obese persons." J.A. 7181 ¶ 13.

Given that both drugs had shown weight loss effects, we conclude that a person of ordinary skill would have been motivated to combine them. In fact,

such persons did so. O'Malley teaches a combination of effective amounts of sustained-release bupropion and naltrexone for minimizing weight gain. Likewise, Dante teaches use of an opioid antagonist, preferably naltrexone, and an antidepressant, including bupropion, for decreasing sugar cravings, noting that naltrexone administration alone led reduced sugar cravings and weight loss in two examples. A person of skill would have understood that a combination for reducing weight gain and decreasing carbohydrate cravings may affect weight loss as well. *See, e.g.,* J.A. 7156 (speculating that success of a weight-loss treatment could be linked to beneficial effects on "food cravings"); 7172 (explaining that patient hunger is relevant to efficacy and outcomes of a weight-loss treatment); 7181 (explaining "obese persons" would benefit from a method for reducing carbohydrate cravings).

Nalpropion suggests that, even in view of these references, a person of skill would not have been motivated to develop bupropion for weight loss (1) because bupropion yielded only a "paltry 2.8% placebo-adjusted weight loss," which was too insignificant to obtain FDA approval as a weight loss drug, Appellee's Br. 41, (2) because bupropion carried a seizure risk, and (3) because its mechanism of action was unknown.

We are not persuaded. Nalpropion argues that bupropion does not possess sufficient weight loss efficacy to obtain FDA approval by itself. But, while bupropion alone may not have been entitled to FDA approval as a weight-loss treatment, "[t]here is no requirement in patent law that the person of ordinary skill be motivated to develop the claimed invention based on a rationale that forms the basis for FDA

approval." *Allergan, Inc. v. Sandoz Inc.,* 726 F.3d 1286, 1292 (Fed. Cir. 2013). "Motivation to combine may be found in many different places and forms; it cannot be limited to those reasons the FDA sees fit to consider in approving drug applications." *Id.* Instead, "[t]he court should consider a range of real-world facts to determine 'whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue.'" *Arctic Cat Inc. v. Bombardier Recreational Prods. Inc.,* 876 F.3d 1350, 1359 (Fed. Cir. 2017) (quoting *Intercontinental Great Brands LLC v. Kellogg N. Am. Co.,* 869 F.3d 1336, 1344 (Fed. Cir. 2017), *cert. denied,* 139 S. Ct. 143 (2018)). The inescapable, real-world fact here is that people of skill in the art *did combine* bupropion and naltrexone for reductions in weight gain and reduced cravings—goals closely relevant to weight loss. Contrary to Nalpropion's view, persons of skill *did combine* the two drugs even without understanding bupropion's mechanism of action but with an understanding that bupropion was well-tolerated and safe as an antidepressant. *See* J.A. 7165 ("The precise mechanism for bupropion SR that is responsible for effects on weight loss is unknown."); *see also* J.A. 7157 (same). Thus, we conclude that skilled artisans would have been motivated to combine the two drugs for weight loss with a reasonable expectation of success.

We next consider the specific language of the claims in relation to the prior art. Claim 1 of the '111 patent requires (1) a sustained-release formulation of bupropion or a pharmaceutically acceptable salt thereof in an amount effective to induce weight loss in an individual; and (2) a sustained- release formulation of naltrexone or a pharmaceutically acceptable salt

thereof in an amount effective to enhance the weight loss effect of the bupropion or salt thereof; (3) in a single oral dosage form fixed combination.[6] Jain discloses 300 and 400 mg per day dosages of sustained-release bupropion as facilitating weight loss, meeting the first limitation. O'Malley discloses a sustained-release formulation of naltrexone administered with bupropion as a "withdrawal attenuating agent," O'Malley col. 2 ll. 59-66, that "enhance[s] the efficacy of the nicotine dependency treatment," *id.* col. 4 ll. 25-33, a treatment designed to minimize weight gain, *id.* col. 8 ll. 45-48. The naltrexone dosages in O'Malley—from 12.5 mg to 150 mg—are amounts effective to enhance the weight loss effects of bupropion. *Id.* col. 5 ll. 46-50.[7] O'Malley also discloses a single oral dosage form of bupropion and naltrexone.

Next, we turn to claims 26 and 31 of the '626 patent. Claim 25, from which both claims 26 and 31 depend, requires administering a weight-loss effective amount of a first and a second compound to treat an individual suffering from overweight or obesity for that condition. The first and second compounds are bupropion

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[6] Actavis argues that the preamble, which recites "a composition for affecting weight loss," is not limiting, while Nalpropion argues that it is limiting because it recites the fundamental purpose of the invention. Appellee's Br. 49. Because neither party asked the district court to construe the preamble, these arguments are waived. *Interactive Gift Exp., Inc. v. Compuserve Inc.,* 256 F.3d 1323, 1346 (Fed. Cir. 2001).

[7] Claim 2 of the '111 patent depends from claim 1, and thus requires an amount of naltrexone effective to enhance the weight loss effect of bupropion. That claim is drawn to about 5 mg to about 50 mg of naltrexone. Thus, about 5 mg to 50 mg of naltrexone constitutes an amount effective to enhance the effect of bupropion. *See* 35 U.S.C. § 112 ¶ 4 (2010).

and naltrexone, and the weight loss effects of the compounds are "enhanced" compared to the administration of either compound alone. Claim 26 adds the requirement that the two drugs be administered together, and claim 31 requires that at least one of the drugs is in a sustained-release formulation and that they are administrated in a single oral dosage form. As with the '111 patent, the combination of O'Malley and Jain meets these requirements, with Jain disclosing effective amounts of sustained-release bupropion for weight loss and O'Malley disclosing its combination with naltrexone in a single dosage form.

Having concluded that every limitation in the claims at issue was met by O'Malley and Jain, we consider objective indicia of nonobviousness. Nalpropion argues that many others tried and failed to find a combination effective for weight loss and that the claimed combination exhibited unexpected results. But the inventors only combined two drugs known to affect weight loss. Both drugs were known to affect weight loss, and combining them for this known purpose as claimed in the patents yields no unpredictable result. *See KSR Int'l Co. v. Teleflex Inc.,* 550 U.S. 398, 416 (2007) ("The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results."). The result—a combination drug that affected weight loss—could not have been unexpected. To the extent Nalpropion maintains that the failure of others supports a finding of nonobviousness, that factor alone cannot overcome the clear record in this case that the combination of the two drugs was known and that both drugs would have been understood to be useful for this purpose.

Because we conclude that claim 1 of the '111 patent and claims 26 and 31 of the '626 patent would have been obvious to a person of skill in the art in view of O'Malley and Jain, we reverse the district court's holding that these claims are not invalid.

Finally, Nalpropion filed a motion to strike Actavis's reply brief. Plaintiff-Appellee Nalpropion Pharms. Inc.'s Motion to Strike, *Nalpropion Pharm. Inc. v. Actavis Labs. FL, Inc.,* No. 18-1221 (Fed. Cir. Dec. 27, 2018), ECF No. 54. We deny this motion as moot.

CONCLUSION

We have considered both parties' remaining arguments and find them unpersuasive. For the reasons detailed above, we hold that the district court did not clearly err in finding claim 11 of the '195 patent not invalid for lack of adequate written description and affirm its judgment in this respect. We reverse, however, the court's judgment that claims 26 and 31 of the '626 patent and claim 1 of the '111 patent are not invalid.

AFFIRMED-IN-PART AND REVERSED-IN-PART

COSTS

No costs.

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

NALPROPION PHARMACEUTICALS, INC.,
Plaintiff-Appellee

v.

ACTAVIS LABORATORIES FL, INC.,
Defendant-Appellant

2018-1221

Appeal from the United States District Court for the District of Delaware in No. 1:15-cv-00451-RGA, Judge Richard G. Andrews.

PROST, *Chief Judge,* dissenting in part.

Today, the majority adds what appears to me to be a new rule to this court's long-standing written description jurisprudence. It holds that a "substantially equivalent" disclosure may satisfy the written description requirement when the relevant claim limitation recites only "resultant dissolution parameters rather than operative claim steps." Majority Op. 12. Respectfully, that is not the law. Premised on my understanding of this court's precedent, I would find claim 11 of the '195 patent invalid for lack of adequate written description. Consequently, I must dissent from Section I of the majority's opinion.

The disputed limitation is the wherein clause directed to the dissolution profile for sustained-release naltrexone, as measured by the USP Apparatus 2 Paddle Method ("USP 2"):

> wherein said sustained-release formulation of naltrexone has an in vitro naltrexone dissolution profile in a dissolution test of USP Apparatus 2 Paddle Method at 100 rpm in a dissolution medium of water at 37° C. of
>
> a) between 39% and 70% of naltrexone released in one hour;
>
> b) between 62% and 90% of naltrexone released in two hours; and
>
> c) at least 99% in 8 hours . . . .

'195 patent col. 31 ll. 11-21 (hereinafter "the USP 2 clause").

The majority and I agree that the essence of the claimed invention is "a method of treating overweight or obesity." Majority Op. 10. We also agree that claim 11 includes one operative step, which relates to orally administering, among other things, a specific amount of sustained- release naltrexone formulation. *Id.*

I part ways with the majority, however, for at least three reasons. First, the USP 2 clause is limiting. Second, the majority's "substantially equivalent" rule is inconsistent with this court's precedent. Third, the district court clearly erred in finding that the '195 patent's written description includes a disclosure "substantially equivalent" to USP 2.

As to the limiting effect of the USP 2 clause, the majority determines that the clause is nonlimiting

because it relates only to the measurement of dissolution data resulting from the oral administration step. *See* Majority Op. 10. This conclusion is wrong. A clause is limiting if, as here, the clause "relate[s] back to and clarif[ies] what is required by the count." *Griffin v. Bertina,* 285 F.3d 1029, 1033 (Fed. Cir. 2002). Indeed, the USP 2 clause does not "merely state the inherent result of performing the manipulative steps." *Id.; compare Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.,* 246 F.3d 1368, 1375 (Fed. Cir. 2001) (concluding a statement directed to the intended result of administering express dosage amounts to be nonlimiting where the result "does not change those amounts or otherwise limit the claim"). Rather, the USP 2 clause "is part of the process itself." *Hoffer v. Microsoft Corp.,* 405 F.3d 1326, 1329-30 (Fed. Cir. 2005).

Specifically, the USP 2 clause clarifies what the claimed invention requires by reciting a property of the claimed naltrexone formulation necessary to "treat[] overweight or obesity." '195 patent col. 31 ll. 5-6. Claim 11 requires the sustained-release naltrexone to be formulated such that it obtains the recited dissolution profile as particularly measured by USP 2—not as generally measured by any method. The '195 patent disclosure confirms this view.

According to the '195 patent, oral dosage forms of sustained-release naltrexone "comprise naltrexone and a sustained-release carrier." *Id.* col. 13 ll. 1-2. Sustained-release carriers, such as hydroxypropylmethyl cellulose ("HPMC") or polyethylene oxide ("Poly-Ox"), are mixed with naltrexone to effect sustained, as opposed to immediate, release. *Id.* col. 13 ll. 1-12, col. 16 ll. 8-26. The amount of sustained-release carrier determines the in vitro release rate (dissolution)

profile of the naltrexone formulation. *Id.* col. 13 ll. 35-45. Thus, the dissolution profile, as measured using USP 2, reflects the amount of sustained-release carrier included in the orally administered naltrexone formulation.

The prosecution history also evidences the material role of the USP 2 clause. In response to an obviousness rejection during prosecution, Applicant argued that, having used a different method, there was no basis to conclude that the prior art inherently disclosed a formulation that falls within the claimed dissolution profile. J.A. 7039 (Prosecution History, Applicant's Remarks). Applicant specifically emphasized the significance of the claimed dissolution profile as performed "under the specific dissolution test conditions recited in the . . . claims." *Id.; see also Hoffer,* 405 F.3d at 1329-30 (stating that a clause cannot be ignored if it is material to patentability).

Applicant did not stop there. Applicant further stated that "there are sustained-release [naltrexone] formulations which fall outside the scope of the . . . claimed dissolution profiles." J.A. 7039. There is no evidence to the contrary in the record. Even during litigation, neither party identified any evidence that a 32 mg dose of any sustained-release naltrexone formulation necessarily contains an amount of sustained-release carrier that inherently generates the claimed USP 2 dissolution profile measurement.

Moreover, and most tellingly, the parties do not even dispute that the USP 2 clause is limiting. Indeed, Appellee expressly agrees that the USP 2 clause is limiting for purposes of infringement. Appellee's sole written description argument is that the '195

patent's disclosure of USP Apparatus 1 Basket Method ("USP 1") provides adequate written description for the USP 2 clause. *See* Oral Arg. at 15:09-33, No. 2018-1221, http://www.cafc.uscourts.gov/oral-argument-recordings ("[F]or purposes of infringement you need to use [USP 2]. But if you look in terms of the 112 issues, . . . the patent is clear that USP 1 and USP 2 are equivalent to one other."). By concluding that the USP 2 clause is nonlimiting, the majority has sua sponte addressed a claim construction argument never presented to the district court.

To the extent that the majority determined that construing the USP 2 clause was necessary to resolve the written description dispute, it should have adopted the district court's undisputed, implied construction, which treated the clause as limiting.[1] *Applied Med. Res. Corp. v. U.S. Surgical Corp.,* 448 F.3d 1324, 1333 (Fed. Cir. 2006) (explaining that this court has "decline[d] to construe [a claim term] in the first instance and appl[ied] the undisputed claim construction adopted by the district court").

As the USP 2 clause is limiting and the original patent disclosure fails to literally or inherently disclose it, the written description inquiry should end there. *PowerOasis, Inc. v. T-Mobile USA, Inc.,* 522 F.3d 1299, 1306 (Fed. Cir. 2008) (explaining that to satisfy

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[1] Although the district court did not explicitly articulate a construction of the USP 2 clause, a reading of its opinion compels the conclusion that it construed the USP 2 clause to have limiting effect. *E.g., Orexigen Therapeutics, Inc. v. Actavis Labs. FL, Inc.,* 282 F. Supp. 3d 793, 801 (D. Del. 2017) ("Claim 11 includes the limitation that the naltrexone have a specific dissolution profile measured 'in a dissolution test of [USP 2] . . . .'").

the written description requirement, "the written description [must] actually or inherently disclose the claim element"). But it does not. After determining that the USP 2 clause is nonlimiting, the majority adopts Appellee's view that disclosure of USP 1 can provide adequate written description support for the USP 2 clause because the two testing methods are "substantially equivalent." Majority Op. 12; *see also id.* at 10-11.

Such a conclusion problematically articulates a new rule for written description. According to the majority, written description for nonlimiting clauses may be satisfied by disclosure that is "substantially equivalent" even though the same disclosure would not be sufficient for limiting clauses. This rule, however narrow, is at odds with this court's precedent.

Written description requires sufficient disclosure to "clearly allow persons of ordinary skill in the art to recognize that the inventor invented what is claimed." *Ariad Pharm., Inc. v. Eli Lilly and Co.,* 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc) (brackets omitted). A substantially equivalent disclosure, even if it would render the claim limitation obvious, cannot satisfy the written description requirement. *See id.* at 1352 ("[A] description that merely renders the invention obvious does not satisfy the requirement."); *Lockwood v. Am. Airlines, Inc.,* 107 F.3d 1565, 1572 (Fed. Cir. 1997) ("The question is not whether a claimed invention is an obvious variant of that which is disclosed in the specification.").

In any event, even if the majority's "substantially equivalent" rule was appropriate, I would still disagree with its affirmance on the written description

issue. In finding that USP 1 and USP 2 are substantially equivalent, the majority overlooks the district court's clear error. Not a shred of record evidence supports this fact-finding. And other record evidence refutes it.

The record contains no evidence showing that the two methods produce the same results. Oral Arg. at 24:04-12 (Q: Do you have positive tests, confirmative testing saying [USP 1 and USP 2] are the same thing? A: No. Neither side submitted any testing data on that point.). Indeed, Appellee's expert, Dr. Treacy, testified that he had formed no opinion about any differences between USP 1 and USP 2. *See* J.A. 11410:24-11411:2.

Instead, the record includes evidence that the two methods do not produce the same results. First, Dr. Soltero, one of the inventors named on the '195 patent, testified that USP 1 and USP 2 results are not comparable. He confirmed that "just because you got a certain profile [using] a USP 1 method, you would not necessarily expect that you would get the same release profile [using] USP 2." *See* J.A. 11319:17-11321:12. The trial court's opinion does not even mention this testimony.

Second, Appellant's expert, Dr. Mayersohn, opined that a skilled artisan would not have understood the two methods to yield the same results. J.A. 11356:22-11357:3. The district court discounted Dr. Mayersohn's testimony, finding that his "theoretical opinion that the methods would yield different results is at odds with his reliance on a prior art reference using [USP 1] to argue that claim 11, which specifies [USP

2], was obvious." *See* Majority Op. 11 (citing *Orexigen,* 282 F. Supp. 3d at 801-02).

The standard for obviousness is not, however, the same as the standard for written description. Based on our precedent, teachings related to USP 1 may render methods using USP 2 obvious, but Dr. Mayersohn's testimony that the two would not produce the same results is nonetheless relevant for written description. *See Ariad,* 598 F.3d at 1352; *Lockwood,* 107 F.3d at 1572.

In a record devoid of evidence showing that USP 1 and USP 2 are "substantially equivalent," the district court clearly erred in disregarding Dr. Soltero's testimony and in discounting Dr. Mayersohn's, which indicate that they are not substantially equivalent.

For the foregoing reasons, I respectfully dissent from Section I.

APPENDIX B

IN THE UNITED STATES DISTRICT COURT FOR THE DISTRICT OF DELAWARE

OREXIGEN THERAPEUTICS, INC., Plaintiff, v. ACTAVIS LABORATORIES FL, INC. Defendant.	Civil Action No. 15-451-RGA

TRIAL OPINION

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Attorneys for Defendant.

October 13, 2017

/s/ Richard G. Andrews

ANDREWS, U.S. DISTRICT JUDGE:

Plaintiff brought this patent infringement action on June 3, 2015, alleging that Defendant had infringed seven of Plaintiff's patents by filing Abbreviated New Drug Application ("ANDA") No. 208043 seeking to enter the market with a generic version of Plaintiff's Contrave product. (D.I. 1). On April 15, 2016, Plaintiff filed a First Amended Complaint alleging infringement of four patents. (D.I. 47). Prior to trial, Plaintiff withdrew one of the four patents (*see* D.I. 182), leaving three patents-in-suit: U.S. Patent Nos. 7,462,626 ("the '626 patent"), 7,375,111 ("the '111 patent"), and 8,916,195 ("the '195 patent"). The Court held a three day bench trial on June 5-7, 2017. (D.I. 178, 179, 180) ("Tr.").

Plaintiff's Contrave product is approved by the Food and Drug Administration ("FDA") for "chronic weight management in adults" who are obese or overweight and who have "at least one weight-related comorbidity," such as type 2 diabetes or hypertension. (D.I. 117-1 at 5, ¶ 4). Contrave is formulated as extended-release tablets with the active ingredients naltrexone hydrochloride and bupropion hydrochloride. (*Id.*, ¶ 3).

Bupropion was first approved by the FDA in 1996 for use as an antidepressant and in 1997 for use in smoking cessation treatment. (Tr. 422:11-13). Bupropion was known to have weight loss effects as early as 1995. (Tr. 422:18-424:11). The efficacy and safety of bupropion for weight loss had been studied extensively prior to 2003, the priority date for the invention claimed in the patents-in-suit. (Tr. 425:10-431:23). Naltrexone is an opioid agonist that is FDA approved for treating drug addiction. (Tr. 432:112-433:10). At least as early as 2002, naltrexone was known to reduce carbohydrate cravings in patients with diabetes. (Tr. 433:21-434:19).

The '626 patent is directed to methods of treating overweight or obesity using a combination of naltrexone and bupropion. Plaintiff asserts that Defendant induces infringement of dependent claims 2, 15, 26, and 31 of the '626 patent. Claims 2 and 15 depend from independent claim 1, which reads:

> 1. A method of treating overweight or obesity, comprising diagnosing an individual as suffering from overweight or obesity by determining said individual has a body mass index of at least 25 kg/m2, and treating said overweight or obesity by administering to said individual a first compound and a second compound in order to treat said overweight or obesity, wherein said second compound is bupropion or a pharmaceutically acceptable salt thereof in an amount effective to induce weight loss in said individual, and said first compound is naltrexone or a pharmaceutically acceptable salt thereof in an amount effective to enhance

> weight loss activity of said bupropion or a pharmaceutically acceptable salt thereof.

('626 patent, claim 1). Dependent claim 2 adds the limitation that the naltrexone and bupropion "are administered together." Dependent claim 15 adds the limitation that the naltrexone and bupropion "are administered in a single oral dosage form."

Claim 26 depends from independent claim 25, which reads:

> 25. A method of treating overweight or obesity, comprising administering a weight loss effective amount of a first and second compound to an individual who has been diagnosed as suffering from overweight or obesity in order to treat said overweight or obesity, wherein said first compound is bupropion, or a pharmaceutically acceptable salt thereof, and said second compound is naltrexone, or a pharmaceutically acceptable salt thereof, and wherein the weight loss activity of said first and second compounds is enhanced compared to the administration of the same amount of either compound alone.

('626 patent, claim 25). Claim 26 adds the limitation that the naltrexone and bupropion "are administered together." Asserted claim 31 depends from claim 30, which is not asserted and which depends from claim 25. Claim 30 adds the limitation that the naltrexone and bupropion "are in a sustained-release formulation." Asserted claim 31 adds the limitation that the naltrexone and bupropion "are administered in a single oral dosage form."

The '111 patent is directed to compositions for use in weight loss treatments comprising a combination of sustained release formulations of bupropion and naltrexone. Plaintiff asserts that Defendant directly infringes claim 1 of the '111 patent. Claim 1 reads:

> 1. A composition for affecting weight loss comprising:
>
> (a) a sustained release formulation of bupropion or a pharmaceutically acceptable salt thereof in an amount effective to induce weight loss in an individual; and
>
> (b) a sustained release formulation of naltrexone or a pharmaceutically acceptable salt thereof in an amount effective to enhance the weight loss effect of the bupropion or salt thereof;
>
> wherein said composition is in a single oral dosage form fixed combination.

('111 patent, claim 1).

The '195 patent is directed to methods of treating overweight or obesity using a combination of naltrexone and bupropion. Plaintiff asserts that Defendant directly infringes claim 11 of the '195 patent. Claim 11 reads:

> 11. A method of treating overweight or obesity having reduced adverse effects comprising orally administering daily about 32 mg of naltrexone and about 360 mg of bupropion, or pharmaceutically acceptable salts thereof, to a person in need thereof, wherein the bupropion or pharmaceutically acceptable salt thereof is

> administered as a sustained-release formulation, wherein the naltrexone or pharmaceutically acceptable salt thereof is administered as a sustained-release formulation, and wherein said sustained-release formulation of naltrexone has an in vitro naltrexone dissolution profile in a dissolution test of USP Apparatus 2 Paddle Method at 100 rpm in a dissolution medium of water at 37° C. of:
>
> a) between 39% and 70% of naltrexone released in one hour;
>
> b) between 62% and 90% of naltrexone released in two hours; and
>
> c) at least 99% in 8 hours;
>
> wherein about 16 mg of said sustained-release formulation of naltrexone or a pharmaceutically acceptable salt thereof is administered twice daily, and about 180 mg of said sustained-release formulation of bupropion or a pharmaceutically acceptable salt thereof is administered twice daily.

('195 patent, claim 11).

Defendant contends that it does not infringe any of the asserted claims. Defendant also argues that claim 11 of the '195 patent is invalid for lack of written description and all asserted claims of the '111 and '626 patents are invalid as obvious in view of the prior art.

I. MOTION TO STRIKE THE GADDE FAX

Plaintiff moves to strike Defendant's exhibits DTX-48 and DTX-180, a fax sent by Dr. Kishore Gadde to

Orexigen on November 19, 2003 ("Gadde Fax" or "Fax"), as inadmissible hearsay. (D.I. 155 at 2). The Fax consists of a table which contains brief descriptions of patients Dr. Gadde treated for obesity in 1997 and 2000. (DTX-180 at GADDE0000010). According to the table, Dr. Gadde treated four patients in 1997 with a combination of fluoxetine and naltrexone and two patients in 2000 with a combination of bupropion and naltrexone. (*Id.*). Dr. Gadde testified at trial that he prepared the table in 2003 "by reviewing the patient charts." (Tr. 715:16-18, 768:19-21). The original patient charts were not produced as evidence in this case. (D.I. 155 at 3).

Defendant argues that the Gadde Fax is not hearsay because it qualifies as an adoptive admission under Federal Rule of Evidence 801(d)(2)(B).[1] (D.I. 159 at 2; Tr. 722:10-12). According to Defendant, Plaintiff shared the data in the Gadde Fax with the FDA to help demonstrate safety and efficacy of the combination of bupropion and naltrexone. (D.I. 159 at 2; Tr. 722:12-19). As support for this contention, Defendant produced a clinical study report submitted to the FDA

[1] In post-trial briefing, Defendant also argued that the Gadde Fax is admissible under Rule 801(d)(1)(B). (D.I. 159 at 6-7). This argument fails at least because Defendant seeks to admit the Gadde Fax itself as substantive evidence, rather than seeking to admit the Fax as a prior statement consistent with Dr. Gadde's testimony in court. Dr. Gadde testified that he had no contemporaneous recollection of the facts of the cases reported on in the Fax. (Tr. 789:6-14). In fact, Dr. Gadde testified directly from the Fax rather than from his independent recollection of the facts and events. (Tr. 715:16-719:10). Defendant cannot invoke Rule 801(d)(1)(B) to gain admission of a prior statement that is not actually offered as a prior consistent statement to in-court testimony.

as part of Orexigen's Investigational New Drug ("IND") Application for fluoxetine or bupropion SR in combination with naltrexone. (DTX-154). In relevant part, the report stated, "When naltrexone was added to fluoxetine or bupropion SR therapy, additional weight loss was observed in 2 of 6 patients; no adverse events other than nausea were reported (K Gadde, personal communication)." (DTX-154 at OREXC0748915).

During trial I found the Gadde Fax to be admissible as an adoptive admission, but allowed the parties to present additional arguments about its admissibility in post-trial briefing. (Tr. 731:1-4). I found that, while "not an absolute certainty," it was "a fair inference" that the paragraph Defendant pointed to was referring to the chart in the Gadde Fax. (Tr. 730:11-14). I also stated that it seemed clear that the paragraph's reference to additional weight loss referred to patients 2 and 3 on the fax, which are patients who received the fluoxetine/naltrexone combination therapy. (Tr. 728:15-729:2).

My opinion that the Gadde Fax is admissible as an adoptive admission has not changed. I think there is sufficient detail in the FDA report to support the inference that the "personal communication" referred to was the Fax. I disagree with Plaintiff's contention that this paragraph was merely a reference to the Fax and a repetition of the hearsay contained in the Fax. (D.I. 155 at 5-6). Orexigen presented this information to the FDA in support of its IND Application. I find it difficult to believe Orexigen would have done so if it did not believe in the trustworthiness of the contents of the communication. As to Plaintiff's argument that Defendant must show that each statement in the Fax

was separately adopted (D.I. 155 at 7), I think this is satisfied by the statement that "additional weight loss was observed in 2 of 6 patients." It seems to me that this refers to the six patients reported in the Fax and I think the only reasonable interpretation is that the Fax was adopted in its entirety.

This does not mean, however, that the Gadde Fax is admissible as substantive evidence of anything that Dr. Gadde did in 1997 or 2000. The parties agreed that any allegations of public use by Dr. Gadde in 2000 would be subject to the corroboration requirement for inventor testimony. (Tr. 950:17-23). Defendant stated at trial that the purpose of Dr. Gadde's testimony and the Gadde Fax was not to prove prior use, but to prove secondary considerations, such as motivation to combine. (Tr. 951:13-17). Defendant argued that motivation to combine was not subject to the corroboration requirement. (Tr. 954:17-955:5). As I discuss below, I disagree. The Gadde Fax is not admissible to show that Dr. Gadde treated patients with the combinations of drugs reported in the Fax in 1997 and 2000, or as evidence of anything that occurred prior to the date the Fax was prepared.

For the foregoing reasons, Plaintiff's Motion to Strike (D.I. 155) is denied. The Gadde Fax is admissible for the limited purpose of showing that Dr. Gadde shared the data reported in the Fax with Orexigen in 2003.

II. WRITTEN DESCRIPTION

The written description requirement contained in 35 U.S.C. § 112, ¶ 1 requires that the specification "clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is

claimed." *Ariad Pharm., Inc., v. Eli Lilly & Co.,* 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc) (alteration in original). "In other words, the test for sufficiency is whether the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Id.* "A party must prove invalidity for lack of written description by clear and convincing evidence." *Vasudevan Software, Inc. v. MicroStrategy, Inc.,* 782 F.3d 671, 682 (Fed. Cir. 2015).

Defendant argues that claim 11 of the '195 patent is invalid for lack of written description because the ranges given for the claimed dissolution profile "were improperly cobbled together" and were measured using a different method than that required by the claim. (D.I. 162 at 10). Specifically, Defendant argues that the lower bounds of the dissolution ranges at one and two hours recited in the claim were not obtained using the USP Apparatus 2 Paddle Method required by the claim. (*Id.* at 10). Defendant further argues that there is no evidence in the specification as to which method was used to obtain the 99% dissolution profile stated in the claim for the eight hour range. (*Id.*). Finally, Defendant argues that the upper bounds of the one and two hour ranges were picked from "a boilerplate paragraph without any sensible reason or industry custom/practice for their random selection." (*Id.*).

Plaintiff responds that simply because the claims draw support from different parts of the specification does not mean that a person of ordinary skill would not believe that the inventor was in possession of the invention. (D.I. 164 at 30). Plaintiff also argues that there is no legal requirement that all claim limitations

be set out in a single place in the specification. (*Id.* at 31). Plaintiff points to the prosecution history, which shows the applicant cited to specific portions of the specification as support for claim 11, resulting in a notice of allowance for this claim. (*Id.*).

Claim 11 of the '195 patent claims a method of treating overweight or obesity using a sustained released formulation of bupropion and naltrexone. Claim 11 includes the limitation that the naltrexone have a specific dissolution profile measured "in a dissolution test of USP Apparatus 2 Paddle Method at 100 rpm in a dissolution medium of water at 37°C." The dissolution profile recited requires "a) between 39% and 70% of naltrexone released in one hour; b) between 62% and 90% of naltrexone released in two hours; and c) at least 99% in 8 hours."

As support for the claimed dissolution profile, Plaintiff points to Table 10 in the specification. (*Id.* at 32). Table 10 provides dissolution data for naltrexone in one embodiment described in the specification. ('195 patent at 19:60-67). Table 10 indicates that, after one hour, 67% of naltrexone was released, after two hours, 85% of naltrexone was released, and after 8 hours, 99% of naltrexone was released. ('195 patent at 20:1-10). These values fall squarely within the ranges in claim 11. Defendant argues that this data is not relevant as it was not obtained using the USP Apparatus 2 method. (D.I. 162 at 11). In response, Plaintiff points to a portion of the specification that it argues constitutes a definition of a "standard dissolution test." (D.I. 164 at 32; '195 patent at 6:49:55).

I agree with Plaintiff that the specification would indicate to a person of ordinary skill that all of the

dissolution data reported in the patent was obtained "using Apparatus 2 . . . at a spindle rotation speed of 100 rpm and a dissolution medium of water, at 37° C., or other test conditions substantially equivalent thereto." ('195 patent at 6:52-55). Plaintiff's expert, Dr. Treacy, testified that a person of ordinary skill would recognize that the inventors had possession of an embodiment representative of the invention, as described in Table 10. (Tr. 660:21-661:1). Dr. Treacy further testified that a person of ordinary skill "would find reasonable support for the claim limitations in the written description," specifically the upper and lower limits for each of the ranges. (Tr. 660:12-20). Dr. Treacy also opined that, in the context of the patent, a person of ordinary skill would understand that the inventors had possession of the claimed invention regardless of whether the USP Apparatus 2 method or a "substantially equivalent" method were used. (Tr. 663:3-9).

Defendant's expert, Dr. Mayersohn, testified at trial that the paddle method and the USP Apparatus 1 basket method were different in that the hydrodynamics were different and that a person of ordinary skill would expect the two methods to yield different results. (Tr. 602:23-604:20). Dr. Mayersohn did not, however, perform any actual tests on the tablets claimed in this patent. (Tr. 640:19-22). Furthermore, in his expert report, Dr. Mayersohn provided an opinion on obviousness for this claim in which he relied on a prior art reference that used the USP Apparatus 1 basket method. (Tr. 637:8-640:13). It seems to me that Dr. Mayersohn's theoretical opinion that the methods would yield different results is at odds with his reliance on a prior art reference using the basket

method to argue that claim 11, which specifies the paddle method, was obvious.

I do not think it matters whether the two methods would yield exactly the same results. I find credible Dr. Treacy's testimony that a person of ordinary skill would understand, in the context of the patent, that the inventors possessed the claimed invention. The embodiments disclosed in a patent are intended to be exemplary and it is clear to me that the inventors possessed at least one embodiment that falls squarely within the claimed ranges, as evidenced by Table 10. Furthermore, Defendant's emphasis on the purported differences between the two methods of measuring dissolution profiles seems to me to be misplaced as even its own expert was willing to favorably compare the two methods when it was to Defendant's benefit to do so. Therefore, whether the dissolution data reported in the specification was obtained using the basket method or the paddle method is not relevant to whether the inventors had possession of the invention.

Defendant also argues that the lower bounds of the one and two hour ranges lack written description support because they were pulled from Table 5, which reports data on specific embodiments which includes different amounts of the polymer excipient hydroxypropylmethyl cellulose ("HPMC"). (D.I. 162 at 12). Defendant contends that the data from the 15% HPMC formulation was "randomly selected" and "improperly picked from amongst a plethora of other possible options." (*Id.* at 12-13). I disagree. As Plaintiff points out, claim 11 calls for a "sustained-release formulation." (D.I. 164 at 34). Both Dr. Mayersohn and Dr. Treacy testified that the data from the 5% and

10% HPMC formulations indicated that both were "essentially immediate release" and the 15% formulation was "the first one . . . where you see a sustained release profile." (Tr. 615:6-19, 655:10-17). For this reason, it seems clear that these are appropriate data points to support the claimed lower bounds for the one and two hour ranges.

Dr. Mayersohn's main criticism of using the data in Table 5 was that there was no eight-hour value and, in his opinion, the data provided indicated that the dissolution profile would plateau and never reach the claimed 99% at eight hours. (Tr. 615:20-616:3). I am not convinced. There is no data provided at all in Table 5 for the dissolution at eight hours. I do not think there is sufficient evidence to support Dr. Mayersohn's plateau theory to a clear and convincing standard for invalidating this patent claim. In contrast, as Plaintiff notes, there is an embodiment reported in Table 10 that has a dissolution profile falling squarely within the claimed ranges. (D.I. 164 at 32).

Defendant also argues that the inventor did not possess the eight-hour limitation by attempting to characterize this limitation as a range, wherein "at least 99%" necessarily "extends up to and includes 100%." (D.I. 162 at 13). Defendant suggests that to show the inventor possessed the invention, Plaintiff must establish written description support "for the upper end of the claimed range above 99%." (*Id.* at 15). I disagree. Dr. Treacy opined that "at least 99%" would be understood by a person of ordinary skill to mean "essentially complete dissolution." (Tr. 653:5-12). I find this testimony credible. It seems clear to me that "at least 99%" means "at least 99%" rather than "between 99% and 100%." I think it is sufficient that the

inventors showed possession by disclosing an embodiment that falls squarely within all of the claimed ranges, including "at least 99%" at eight hours.

Defendant also criticizes the upper bounds of the one and two hour ranges as lacking written description support because these bounds come from "a boilerplate paragraph containing multiple theoretical ranges." (D.I. 162 at 14). As an initial matter, there is no definitive evidence that these ranges were "theoretical." More importantly, I see nothing odd or invalidating about the inventors looking to different tables of dissolution data and other places in the specification to determine the ranges for the claimed dissolution profile. A single test on a single tablet could provide only a single data point at each time; rather, multiple tests are necessarily required to establish a range.

Defendant suggests that all of the purported shortcomings it has identified in the disclosure of the claimed ranges necessarily lead to the conclusion that the patent fails to provide "blazemarks" that would direct a person of ordinary skill to select those specific bounds. (D.I. 162 at 15). The cases Defendant cites to support for this failure do not support its position. (*Id.* at 9). Most of Defendant's cases dealt with situations where an inventor had disclosed a large genus of possible compounds. *Fujikawa v. Wattanasin,* 93 F.3d 1559, 1571 (Fed. Cir. 1996) ("simply describing a large genus of compounds is not sufficient to satisfy the written description requirement as to particular species or sub-genuses"); *Boston Sci. Corp. v. Johnson & Johnson,* 647 F.3d 1353, 1367 (Fed. Cir. 2011) (finding lack of written description where patent claimed "rapamycin or a macrocyclic triene analog thereof" but

specification "fail[ed] to disclose even a single member of either the genus of 'analogs' of rapamycin, or the more specific genus of 'macrocyclic triene analogs' of rapamycin"); *In re Ruschig,* 379 F.2d 990, 994 (C.C.P.A. 1967) (finding lack of written description where disclosure of genus encompassed "half million compounds within the scope of the broadest claim"). The instant case is not one of an inventor disclosing a large genus without any disclosure that certain of the species within the genus are preferred. I hold that Defendant has not proven by clear and convincing evidence that claim 11 of the '195 patent is invalid for lack of written description.

III. OBVIOUSNESS

Defendant argues that claims 26 and 31 of the '626 patent and claim 1 of the '111 patent are invalid as obvious over the prior art.[2] (D.I. 162 at 22, 27-28). Specifically, Defendant argues that a person of ordinary skill in the art would have been motivated to combine the teachings of the Jain and O'Malley references to administer the combination of naltrexone and bupropion for treating overweight and obesity with a reasonable expectation of success. (*Id.* at 28).

A. Legal Standard

A patent claim is invalid as obvious "if the differences between the subject matter sought to be patented and the prior art are such that the subject

[2] As I discuss below, because I find that claims 26 and 31 of the '626 patent are valid and infringed, it is unnecessary for me to decide whether claims 2 and 15 are infringed. I find it equally unnecessary, therefore, to decide whether claims 2 and 15 are valid.

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; *see also KSR Int'l Co. v. Teleflex Inc.,* 550 U.S. 398, 406-07 (2007). The determination of obviousness is a question of law with underlying factual findings. *See Kinetic Concepts, Inc. v. Smith & Nephew, Inc.,* 688 F.3d 1342, 1359-60 (Fed. Cir. 2012). "The underlying factual inquiries include (1) the scope and content of the prior art; (2) the differences between the prior art and the claims at issue; (3) the level of ordinary skill in the art; and (4) any relevant secondary considerations . . . ." *Western Union Co. v. MoneyGram Payment Sys., Inc.,* 626 F.3d 1361, 1370 (Fed. Cir. 2010) (citing *Graham v. John Deere Co.,* 383 U.S. 1, 17-18 (1966)).

A court is required to consider secondary considerations, or objective indicia of nonobviousness, before reaching an obviousness determination, as a "check against hindsight bias." *See In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.,* 676 F.3d 1063, 1078-79 (Fed. Cir. 2012). Relevant secondary considerations include commercial success, long felt but unsolved needs, failure of others, praise, unexpected results, and copying, among others. *Graham,* 383 U.S. at 17-18; *Ruiz v. A.B. Chance Co.,* 234 F.3d 654, 662-63 (Fed. Cir. 2000); *Tex. Instruments, Inc. v. U.S. Int'l Trade Comm'n,* 988 F.2d 1165, 1178 (Fed. Cir. 1993). Secondary considerations of nonobviousness are important because they "serve as insurance against the insidious attraction of the siren hindsight...." *W.L. Gore & Assocs., Inc. v. Garlock, Inc.,* 721 F.2d 1540, 1553 (Fed. Cir. 1983).

A patentee is not required to present evidence of secondary considerations. *See Prometheus Labs., Inc. v. Roxane Labs., Inc.,* 805 F.3d 1092, 1101 (Fed. Cir. 2015). That said, if the patent challenger establishes a prima facie case of obviousness, "the patentee would be well advised to introduce evidence sufficient to rebut that of the challenger." *Id.* (quoting *Pfizer, Inc. v. Apotex, Inc.,* 480 F.3d 1348, 1360 (Fed. Cir. 2007)). There must be enough evidence, however, for a finding that a given secondary consideration exists by a preponderance of the evidence. *See Apple, Inc. v. Samsung Elec. Co., Ltd.,* 839 F.3d 1034, 1053 (Fed. Cir. 2016) (en banc). If there is, then the probative value of each secondary consideration will be considered in light of the evidence produced. That does not mean, though, that the burden of persuasion on the ultimate question of obviousness transfers to the proponent of the secondary consideration. *Pfizer, Inc.,* 480 F.3d at 1359. That burden stays always with the patent challenger. *Id.* at 1359-60.

A party asserting that a patent is invalid as obvious must "show by clear and convincing evidence that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so." *Pfizer, Inc. v. Apotex, Inc.,* 480 F.3d 1348, 1361 (Fed. Cir. 2007). That "expectation of success need only be reasonable, not absolute." *Id.* at 1364. "Whether an ordinarily skilled artisan would have reasonably expected success .... is measured as of the date of the invention[] . . . ." *Amgen Inc. v. F. Hoffman-La Roche Ltd,* 580 F.3d 1340, 1362 (Fed. Cir. 2009).

B. Findings of Fact

1. The level of ordinary skill in the art is a person with a Ph.D. in the pharmaceutical sciences or related field with at least three years of experience in pharmaceutical chemistry or drug development. Such a person would have access to researchers and clinicians as part of a project team. (Tr. 651:3-17, 587:19-588:6, 589:15-590:6).
2. The '111 and '626 patents are entitled to a priority date of no later than April 21, 2004, the filing date of U.S. Application No.10/828,795, which matured into the '111 and '626 patents.
3. The Gadde Fax is not prior art.
4. Jain and O'Malley are prior art.
5. Jain and O'Malley do not teach a person of ordinary skill in the art the combination of bupropion and naltrexone for the treatment of obesity or overweight.
6. The combination of bupropion and naltrexone for the treatment of obesity or overweight as disclosed in claims 26 and 31 of the '626 patent and claim 1 of the '111 patent would not have been obvious to a person of ordinary skill in the art.

C. Conclusions of Law

1. Priority Date of the '111 and '626 Patents

The '111 and '626 patents both claim priority to U.S. Provisional Application No. 60/466,838 ("the '838 provisional application"), filed on April 29, 2003. ('111 patent, cover; '626 patent, cover). Defendant asserts in post-trial briefing that Plaintiff failed to prove that the '838 provisional application "provided an

adequate, enabling written description sufficient to demonstrate that the asserted claims are entitled to the '838 provisional's filing date." (D.I. 162 at 16). Defendant appears to be suggesting that Plaintiff had an affirmative duty to come forward with evidence supporting its claim to priority. I disagree. While the burden of establishing entitlement to the priority date of a provisional application rests with the party claiming priority, *see, e.g., PowerOasis, Inc. v. T-Mobile USA, Inc.,* 522 F.3d 1299, 1305 (Fed. Cir. 2008), Plaintiff need not have met that burden in this case.

As an initial matter, a defendant raising a defense of invalidity based on anticipating prior art "has the burden of going forward with evidence that there is such anticipating prior art." *Tech. Licensing Corp. v. Videotek, Inc.,* 545 F.3d 1316, 1327 (Fed. Cir. 2008). Once the defendant has met its burden, the plaintiff "has the burden of going forward with evidence either that the prior art does not actually anticipate, or . . . that it is not prior art because the asserted claim is entitled to the benefit of a filing date prior to the alleged prior art." *Id.*

Here, Defendant did not come forward with prior art that would cause Plaintiff to present evidence that it is entitled to claim the priority date of its provisional application. First, Defendant's arguments that the '111 and '626 patents are invalid are limited to obviousness and lack of written description. (*See generally* D.I. 153). Defendant does not argue the '111 and '626 patents are invalid as anticipated by any prior art reference. Second, after the pretrial conference, Defendant represented to the Court that it would rely on one specific combination of references to support its obviousness defense as to the '111 and '626 patents. (*See*

D.I. 123). That combination consisted of Jain, a peer reviewed paper from 2002, and O'Malley, a patent that issued on April 1, 2003. Defendant identified no other prior art references to support its obviousness defense, and in particular, none between April 29, 2003 and April 21, 2004. Thus, there was no need for Plaintiff to present evidence that it was entitled to an earlier priority date in order to prevent a particular reference from being treated as prior art. Further, although Defendant referred to Gadde in its letter to the Court (*id.* at 2, 5), Defendant did not indicate that it would rely upon the Gadde Fax as prior art,[3] and in any event, for the reasons stated below, I find that the Gadde Fax does not constitute prior art. Whether the '111 and '626 patents are entitled to the priority date of a provisional application is therefore immaterial under the circumstances of this case.

2. Scope and Content of the Prior Art

i. The Gadde Fax

Defendant argues that Dr. Gadde's work in 2000 treating patients with the combination of naltrexone and bupropion for weight loss, as documented in the Gadde Fax, constitutes prior art. (D.I. 162 at 31). I

[3] That Defendant did not seek to rely on the Gadde Fax as prior art is further supported by Defendant's representations at the pretrial conference on May 15, 2017. At the conference, in connection with Defendant's Motion *in Limine* #3, I asked Defendant whether it would "be relying on some art that is dated between April 29th of 2003 and April 21st of 2004." (D.I. 138 at 75:11-15). Defendant responded that it would drop that motion in light of my request that it identify the specific prior art on which it intended to rely. (*Id.* at 75:17-22). Accordingly, I dismissed Defendant's Motion *in Limine* #3 as moot. (*Id.* at 75:23-24).

disagree. The contents of the Gadde Fax, the purported treatment of six patients in 1997 and 2000, were not corroborated at trial. (Tr. 950:17-951:3). Defendant suggests that no corroboration was necessary "because Dr. Gadde is a nonparty inventor with no interest in this litigation." (D.I. 162 at 31 n.7). It is true that the Federal Circuit has held that "corroboration is required only when the testifying inventor is asserting a claim of derivation or priority of his or her invention and . . . stands to directly and substantially gain by his or her invention being found to have priority over the patent claims at issue." *Thomson, S.A. v. Quixote Corp.,* 166 F.3d 1172, 1176 (Fed. Cir. 1999). The problem for Defendant in this case, however, is that Dr. Gadde did not testify to any independent recollection of any of the facts of the treatments he administered in 1997 or 2000. Rather, Dr. Gadde testified directly from the 2003 Fax. Dr. Gadde's 1997 and 2000 treatments, therefore, are not themselves prior art. The Gadde Fax is not evidence of anything more than the fact that Dr. Gadde shared with Orexigen the contents of the Fax in 2003.

ii. Jain

Jain is a peer reviewed paper published in 2002. (DTX-011). There is no dispute that Jain is prior art. Jain discloses a placebo-controlled study of sustained release bupropion for reducing weight and depressive symptoms in obese patients. (DTX-11, p. 1049). Jain reports a placebo adjusted weight loss of 2.8%. (*Id.*; Tr. 852:23-24). Jain does not discuss naltrexone, nor does it suggest combining bupropion with naltrexone or any other drug. (Tr. 853:17-23). Jain further discloses that the mechanism of action of bupropion for

weight loss was unknown. (DTX-11, p. 1055; Tr. 854:9-17).

iii. O 'Malley

O'Malley is a U.S. Patent that issued on April 1, 2003. (DTX-18, cover). O'Malley issued from an application filed on September 16, 1999. (*Id.*). There is no dispute that O'Malley is prior art. O'Malley discloses the use of an opioid antagonist, such as naltrexone, during smoking cessation to minimize weight gain. (*Id.* at 1:14-21). O'Malley also discloses that the opioid antagonist may be administered "in combination with at least one withdrawal attenuating agent... such as clonidine, acamprosate, antihypertensives, antidepressants, antianxiety agents, agents which alter serotonergic function or other agents." (*Id.* at 4:25:33). One of the antidepressants disclosed in O'Malley is bupropion. (*Id,* claims 1, 4, and 19).

3. Comparing Prior Art and Claimed Subject Matter

Defendant argues that it would have been obvious to a person of ordinary skill in the art to combine bupropion and naltrexone for treating overweight and obesity because both bupropion and naltrexone were known to cause weight loss. (D.I. 162 at 17). Defendant further argues that the combination of bupropion and naltrexone for the purposes of weight loss had also been disclosed prior to the priority date of the '111 and '626 patents. (*Id.* at 18).

Plaintiff responds by arguing that Defendant's obviousness analysis suffers from impermissible hindsight bias. (D.I. 164 at 15). Plaintiff argues that "there were dozens of different biological targets for

weight loss with a wide range of pharmacological agents that could be considered for each of those targets." (*Id.*). Plaintiff contends that Defendant "starts with bupropion because the ultimate invention had bupropion," and argues that assuming a person of ordinary skill "would necessarily focus on improving bupropion" constitutes improper hindsight bias. (*Id.*).

Defendant's expert, Dr. Ahima, opined that Jain disclosed that sustained release bupropion was effective and well-tolerated. (Tr. 430:22-431:2). Plaintiff's expert, Dr. Seeley, disagreed, pointing to the "relatively modest" placebo-adjusted weight loss of 2.8%. (Tr. 852:22-24). This modest weight loss was insufficient to meet FDA requirements of five percent placebo adjusted weight loss. (Tr. 851:5-11). Dr. Seeley also testified that bupropion was "known to have seizure risks." (Tr. 853:3-16). Defendant cites to additional prior art disclosing that bupropion was effective for weight loss, including papers by Anderson and Gadde. (D.I. 162 at 23; Tr. 425:16-426:21,428:3-17; DTX-9; DTX-10). Dr. Seeley responded by pointing to a statement in the Gadde reference that the "seizure risks complicates [bupropion's] use in obesity." (Tr. 877:7-8; DTX-9, p.550). The Gadde paper concludes that, "Alternative norepinephrine and dopamine uptake inhibitor drugs should be investigated as adjunctive therapies in weight management." (Tr. 877:8-11; DTX-9, p.550). Dr. Seeley opined that a person of ordinary skill would understand the Gadde reference as "teach[ing] away from using bupropion as a weight loss therapy." (Tr. 877:14-17).

Dr. Seeley also testified to the many different biological targets for treating obesity. (Tr. 849:17-850:23; PTX-112). Dr. Seeley opined that each of

these biological targets would involve different pharmacological agents. (Tr. 850:17-23). According to Dr. Seeley, the limited effectiveness of bupropion, combined with the fact that the mechanism of action of bupropion was unknown, would discourage a person of ordinary skill from considering bupropion as a starting point in developing a new weight loss drug. (Tr. 854:6-22).

I agree with Plaintiff that Defendant's suggestion that bupropion would be an obvious choice for further study in the treatment of overweight and obesity suffers from impermissible hindsight bias. It seems clear that the weight loss effects of bupropion were known to be relatively modest at best. There is also no dispute that the prior art references reported potential risks associated with bupropion, including the risk of seizure. Based on the lack of knowledge of the mechanism of action, combined with the modest effectiveness, I do not think a person of ordinary skill would have found bupropion to be an obvious starting point for further study.

Defendant next argues that it would have been obvious to combine bupropion with naltrexone to enhance bupropion's weight loss effects. (D.I. 162 at 18). According to Defendant, naltrexone was known to cause weight loss and the combination of bupropion and naltrexone had already been used for weight loss. (*Id.* at 17-18). Plaintiff responds that the literature does not disclose that naltrexone alone was effective for weight loss. (D.I. 164 at 18). Plaintiff further argues that the prior art references Defendant cites in support of the combination do not actually disclose the use of the combination for weight loss. (*Id.* at 19).

Defendant relies on the Atkinson and Bernstein references as support for its argument that naltrexone was known to cause weight loss. (D.I. 162 at 17; Tr. 440:4-21, 438:12-20). Dr. Ahima testified that Atkinson disclosed "a small but significant weight loss in women, not the men" in a study of sixty obese patients given naltrexone for eight weeks. (Tr. 440:15-19; DTX-97, p.419). Dr. Ahima further testified that Bernstein disclosed "significant reductions in carbohydrate cravings" in patients treated with naltrexone. (Tr. 438:12-20; DTX-13 at ¶15).

Plaintiff's expert, Dr. Seeley, pointed out that Bernstein does not disclose weight loss, only curbing carbohydrate cravings. (Tr. 878:13-21). Dr. Seeley further testified that Atkinson disclosed a body weight increase in men taking naltrexone. (Tr. 881:1-18). According to Dr. Seeley, a person of ordinary skill reading Defendant's prior art references would conclude that "naltrexone is not a very effective weight loss agent by itself." (Tr. 882:3-9). Dr. Seeley further opined that the references "teach away from the use of naltrexone." (Tr. 882:10-12).

I agree with Plaintiff that the prior art cited by Defendant does not teach a person of ordinary skill that naltrexone was effective for weight loss. The Bernstein reference in particular was not directed to weight loss and did not disclose weight loss effects of naltrexone. I do not think a disclosure of effectiveness for curbing carbohydrate cravings, without more, would inform a person of ordinary skill that naltrexone was effective for weight loss in overweight or obese individuals. Furthermore, Atkinson's disclosure of a small weight loss in women is counterbalanced by its disclosure of an increase in body weight

in men. I do not think either of these references, individually or in combination, teaches a person of ordinary skill that naltrexone is effective for weight loss.

Finally, Defendant argues that the prior art disclosed the use of the combination of bupropion and naltrexone for weight loss. (D.I. 162 at 18). Defendant cites to the Dante and O'Malley patents as support for this contention. (*Id.*; DTX-16; DTX-18). Dr. Ahima testified that Dante discloses the use of the combination "decreases cravings for sugar and carbohydrates." (Tr. 445:10-18). Dr. Ahima further testified that the combination of bupropion and naltrexone was disclosed in O'Malley as effective for reducing weight gain during smoking cessation treatment. (Tr. 448:22-449:17).

Plaintiff responds by pointing out that neither of these references disclose the use of the combination of bupropion and naltrexone for weight loss. (D.I. 164 at 19). Dr. Seeley testified that Dante disclosed compositions and methods of treatment for depression, not weight loss. (Tr. 869:21-870:3; DTX-16). According to Dr. Seeley, Dante does not disclose weight loss using a combination of bupropion and naltrexone, Dante does not disclose naltrexone enhancing bupropion's weight loss effectiveness, and the only discussion related to weight management in Dante is of weight gain associated with tricyclic antidepressants, a different category of antidepressants than bupropion. (Tr. 870:7-23).

Dr. Seeley further testified that O'Malley is directed to smoking cessation treatments, not weight loss. (Tr. 856:14-857:5). Dr. Seeley explained that O'Malley does not contain a single disclosure of weight loss. (Tr.

857:3-5). Rather, O'Malley discloses a single example of minimizing weight gain during smoking cessation therapy and that the single example did not use the combination of naltrexone and bupropion. (Tr. 857:6-22). Dr. Seeley explained that a person of ordinary skill would read O'Malley to disclose that bupropion was used to treat the depressive symptoms smokers have when they stop smoking. (Tr. 858:14-859:4). Dr. Seeley further explained that naltrexone was used "as an adjunct for smoking cessation therapy . . . to block [the] rewarding ability [of nicotine], making it less likely that you're going to pick up a cigarette again." (Tr. 859:17-23). According to Dr. Seeley, there is no disclosure of naltrexone enhancing bupropion's weight loss effects. (Tr. 860:7-861:17). Rather, the only enhancement disclosed in O'Malley is the enhancement of smoking cessation treatments. (Tr. 863:6-20).

I find Dr. Seeley's testimony and explanations credible. I do not think that Dante and O'Malley teach a person of ordinary skill that the combination of naltrexone and bupropion is effective for weight loss. Neither of these references teach a person of ordinary skill anything about weight loss and neither of them indicate that naltrexone enhances bupropion's effectiveness for weight loss. Defendant's argument, it seems to me, is a classic case of hindsight bias. Defendant begins with the combination Plaintiff ultimately patented and then seeks to justify that combination by combining prior art references that simply would not guide a person of ordinary skill to choose this combination.

Defendant argues that a person of ordinary skill would have been motivated to combine the teachings

of Jain and O'Malley to arrive at the combination of bupropion and naltrexone for weight loss. (D.I. 162 at 28). Defendant's rationale is based on a person of ordinary skill reaching the conclusion that naltrexone was effective for weight loss and that the combination had been previously used in connection with weight loss. (*Id.*). I have already determined that neither of these conclusions are supported by Defendant's prior art references. It seems clear that the prior art disclosed that naltrexone was not effective for weight loss, at least because it caused weight gain in the men involved in the study. Furthermore, Defendant's prior art does not disclose the use of the combination for weight loss, nor does it disclose any enhancement of bupropion's effectiveness for weight loss. I fail to see how the combination of Jain and O'Malley, in the absence of impermissible hindsight bias, would motivate a person of ordinary skill to pursue the combination of bupropion and naltrexone for weight loss.

As I have determined that the Gadde Fax is not prior art and cannot serve as evidence of prior use by Dr. Gadde, I need not consider whether the disclosure of his alleged treatment of two patients in 2000 with the combination of bupropion and naltrexone with "questionable benefit" and "no additional benefit" would have served as motivation to combine or would have provided a reasonable expectation of success.

4. Secondary Considerations

"[S]econdary considerations, when present, must be considered in determining obviousness." *Ruiz,* 234 F.3d at 667; *see also Cyclobenzaprine,* 676 F.3d at 1076 ("[E]vidence on these secondary considerations is to be taken into account *always,* not just when the

decisionmaker remains in doubt after reviewing the art." (quoting *Cable Elec. Prods, v. Genmark, Inc.,* 770 F.2d 1015, 1026 (Fed. Cir. 1985))).

Plaintiff presented evidence of unexpected results and failure of others. (D.I. 164 at 27). Plaintiff argues that the synergistic effect of the combination treatment was unexpected based on what was known from the prior art about using the two drugs individually for weight loss. (*Id.*). Defendant criticizes the single study Plaintiff points to as not being probative of non-obviousness because "it is not commensurate with the scope of the asserted claims." (D.I. 162 at 33). According to Defendant, the claims do not require synergy, only that naltrexone enhance the effectiveness of bupropion. (*Id.*). Defendant further argues that the study only showed synergy for 400 mg of bupropion with 36 mg of naltrexone and that the other combinations reported in the study were "merely additive." (*Id.*). I am not persuaded. As I concluded above, a person of ordinary skill would not have expected the combination of bupropion and naltrexone to have any enhanced effectiveness compared to bupropion alone. Therefore, it seems to me that even a limited study showing synergy for some combinations of the two drugs would necessarily constitute unexpected results.

Plaintiff argues that there had been "numerous failures in the field of safe and effective obesity medications." (D.I. 164 at 27). Plaintiff presented evidence that "by the time of invention . . . there were only two FDA drugs approved for the long-term treatment of obesity" and "at least seven other drugs that were being developed for the treatment of obesity had failed." (*Id.* at 28). Defendant counters that, rather than

showing failure of others, the record shows evidence of success of others. (D.I. 162 at 34). Defendant again cites to the work of O'Malley, Dante, and Dr. Gadde as support for its contention that others had been successful in using the combination of naltrexone and bupropion for weight loss. (*Id.*). As I stated above, I disagree that there was any disclosure in O'Malley or Dante showing the use of the combination for weight loss and I am dubious about the claim that Dr. Gadde's results in treating two patients showed success. Defendant also argues that "there were and are a number of FDA-approved weight loss drugs" that are more effective and that carry a lower risk of side effects than the bupropion-naltrexone combination. (*Id.*). Defendant's claim that there were "a number of" other weight loss drugs is belied by the fact that it can only name two other approved weight loss drugs. (*Id.*). I do not think these two other drugs rebut Plaintiff's showing that many others had tried and failed to obtain FDA approval for weight loss drugs.[4]

For the reasons given above, I find that Defendant has not met its burden of proving by clear and convincing evidence that claims 26 and 31 of the '626 patent and claim 1 of the '111 patent are obvious.

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[4] In post-trial briefing, Defendant for the first time argued that Plaintiff's Contrave product has not been commercially successful and that Dr. Gadde's 2000 treatment of two patients constitutes simultaneous invention. (D.I. 162 at 35-36). As Defendant failed to make these arguments at trial, I decline to consider either of them. Even if I were to consider them, I would be dubious about the merits of both arguments.

IV. INFRINGEMENT

Plaintiff asserts that Defendant directly infringes claim 1 of the '111 patent and indirectly infringes claim 11 of the '195 patent and claims 2, 15, 26, and 31 of the '626 patent. During discovery, Defendant never alleged that its proposed ANDA product did not meet the following claim limitations: 1) "bupropion . . . effective to induce weight loss" in the '626 and '111 patents; 2) "naltrexone . . . effective to enhance the weight loss effect of the bupropion" in the '626 and '111 patents; and 3) "sustained release" in the '111 and '195 patents. (D.I. 129 at 4). In the pre-trial order, Defendant attempted to raise new non-infringement defenses, including by alleging failure of proof of these three limitations. (*Id.* at 3). In an order dated May 19, 2017, I held that Defendant had waived the right to contest these three limitations. (*Id.* at 5).

A. Legal Standard

A patent is infringed when a person "without authority makes, uses, offers to sell, or sells any patented invention, within the United States . . . during the term of the patent . . . ." 35 U.S.C. § 271(a). A two-step analysis is employed in making an infringement determination. *See Markman v. Westview Instruments, Inc.,* 52 F.3d 967, 976 (Fed. Cir. 1995) (en banc), *aff'd,* 517 U.S. 370 (1996). First, the court must construe the asserted claims to ascertain their meaning and scope. *See id.* The trier of fact must then compare the properly construed claims with the accused infringing product. *See id.* This second step is a question of fact. *Bai v. L & L Wings, Inc.,* 160 F.3d 1350, 1353 (Fed. Cir. 1998). "Literal infringement of a claim exists when every limitation recited in the claim is

found in the accused device." *Kahn v. Gen. Motors Corp.,* 135 F.3d 1472, 1477 (Fed. Cir. 1998). "If any claim limitation is absent from the accused device, there is no literal infringement as a matter of law." *Bayer AG v. Elan Pharm. Research Corp.,* 212 F.3d 1241, 1247 (Fed. Cir. 2000). The patent owner has the burden of proving infringement by a preponderance of the evidence. *See SmithKline Diagnostics, Inc. v. Helena Labs. Corp.,* 859 F.2d 878, 889 (Fed. Cir. 1988).

35 U.S.C. § 271(b) provides that "[w]hoever actively induces infringement of a patent shall be liable as an infringer." 35 U.S.C. § 271(b). "In order to prevail on an inducement claim, the patentee must establish first that there has been direct infringement, and second that the alleged infringer knowingly induced infringement and possessed specific intent to encourage another's infringement." *ACCO Brands, Inc. v. ABA Locks Mfrs. Co.,* 501 F.3d 1307, 1312 (Fed. Cir. 2007) (internal quotation marks omitted). In other words, "inducement requires evidence of culpable conduct, directed to encouraging another's infringement, not merely that the inducer had knowledge of the direct infringer's activities." *DSU Med. Corp. v. JMS Co.,* 471 F.3d 1293, 1306 (Fed. Cir. 2006) (en banc). "[S]pecific intent may be inferred from circumstantial evidence where a defendant has both knowledge of the patent and specific intent to cause the acts constituting infringement." *Ricoh Co. v. Quanta Computer Inc.,* 550 F.3d 1325, 1342 (Fed. Cir. 2008). "[L]iability for induced infringement can only attach if the defendant knew of the patent and knew as well that 'the induced acts constitute patent infringement.'" *Commil USA, LLC v. Cisco Sys., Inc.,* 135 S. Ct. 1920, 1926 (2015) (quoting *Global-Tech Appliances, Inc. v. SEB*

S.A., 131 S. Ct. 2060, 2068 (2011)). The knowledge requirement may be satisfied by showing actual knowledge or willful blindness. *See Global-Tech,* 131 S. Ct. at 2068 (2011).

In Hatch-Waxman cases alleging that a proposed drug label will induce infringement by physicians, "The pertinent question is whether the proposed label instructs users to perform the patented method." *AstraZeneca LP v. Apotex, Inc.,* 633 F.3d 1042, 1060 (Fed. Cir. 2010). "The label must encourage, recommend, or promote infringement." *Takeda Pharm. USA, Inc. v. West-Ward Pharm. Corp.,* 785 F.3d 625, 631 (Fed. Cir. 2015). "The mere existence of direct infringement by physicians, while necessary to find liability for induced infringement, is not sufficient for inducement." *Id.* Rather, "specific intent and action to induce infringement must be proven." *Id.* Even where a proposed label does not explicitly track the language of a claimed method, a package insert containing directives that will "inevitably lead some consumers to practice the claimed method" provides sufficient evidence for a finding of specific intent. *See AstraZeneca,* 633 F.3d at 1060; *see also Abraxis Bioscience, Inc. v. Navinta, LLC,* 630 F. Supp. 2d 553, 570 (D.N.J. 2009) ("Statements in a package insert that encourage infringing use of a drug product are alone sufficient to establish intent to encourage direct infringement."), *rev'd and vacated on other grounds,* 625 F.3d 1359 (Fed. Cir. 2010).

B. Divided Infringement

Defendant contends that all of the asserted claims of the '626 patent require two steps, diagnosing and administering, that are each performed by a different

actor, the doctor and the patient. (D.I. 172 at 8-10). According to Defendant, since the doctor diagnoses and the patient administers, there can be no infringement of these claims unless the patient is under the "control" of the doctor. (*Id.* at 11-14).

As an initial matter, I find that claims 26 and 31, which depend from claim 25, of the '626 patent involve the single step of administering the drug to a patient who has already been diagnosed. Defendant attempts to create an additional step in this method claim based on the fact that claim 25 requires that the drug is to be administered "to an individual who has been diagnosed as suffering from overweight or obesity." According to Defendant, "an obesity/overweight diagnosis is an explicit requirement of all of the '626 claims that will always be performed before the administering step." (D.I. 172 at 10) (emphasis omitted). I agree that a diagnosis is required, but I disagree that this comprises a step in the method claim. A plain reading of this claim limitation indicates that the individual will already be diagnosed prior to the method being performed. The method itself requires only the single step of administering the drug.

I also disagree with Defendant's assertion that Plaintiff "unequivocally admitted that the asserted claims of the '626 patent require a diagnosing step." (D.I. 172 at 10). Plaintiff made no such admission. Rather, Plaintiff stated only that some of the claims require "diagnosing" while other claims require "an individual who has been diagnosed." (D.I. 131, Ex. 17B at 1). This restatement of the precise language of the claims is not an admission of anything.

There is no dispute that claims 2 and 15, which both depend from claim 1, involve both a diagnosing step and an administering step. There is also no dispute that the diagnosing step is performed by the doctor, but the administering step, which I have construed as "delivering into the body" is performed by the patient, who takes the pills each day outside of the presence of the doctor. The parties dispute whether the patient's actions in self-administering the drug are attributable to the physician who performed the diagnosing step. I do not think it is necessary for me to decide this issue. Having found that all of the asserted claims of the '626 patent are not invalid and that claims 26 and 31 are infringed, I think the question of divided infringement presented by claims 2 and 15 is moot. I cannot conceive of any circumstances in which an additional finding of either infringement or non-infringement of claims 2 and 15 would have any impact on the outcome of this case. Therefore, I decline to decide whether the administering step in independent claim 1 is attributable to the physician.

C. Infringement of the '111 Patent

Plaintiff asserts that Defendant directly infringes claim 1 of the '111 patent. Prior to trial, the only non-infringement argument raised by Defendant as to the '111 patent was that it could not be infringed because it was invalid. (D.I. 129 at 3). By order dated May 19, 2017, I held that Defendant would not be allowed to raise new non-infringement arguments for the first time at trial. (*Id.*).

1. Findings of Fact

1. Defendant has not disputed infringement of claim 1 of the '111 patent. (Tr. 98:24-99:3, 499:8-17).

2. Defendant's ANDA Product is a composition for affecting weight loss. (PTX-022.0001; Tr. at 97:14-23).

3. Defendant's ANDA Product contains sustained-release naltrexone and bupropion. (PTX-022.0002; Tr. at 92:8-14, 95:14-96:8).

4. Defendant's ANDA Product contains bupropion in an amount effective to induce weight loss. (PTX-022.0005-.0006, .0028, .0039-.0040; Tr. 77:6-23, 90:7-21, 93:11-19, 97:14-23, 152:23-153:3).

5. Defendant's ANDA Product contains naltrexone in an amount effective to enhance weight loss activity of the bupropion. (PTX-022.0005, .0028, .0039-.0040; Tr. 78:2-14, 78:19-79:18, 90:7-91:12, 92:15-93:8, 93:11-19; 94:10-23, 97:24-98:13, 114:11-24, 152:23-153:3).

6. Defendant's ANDA Product is a single oral dosage form fixed combination. (PTX-022.0002; Tr. 91:13-92:14, 93:8-10, 95:4-13, 98:14-23).

7. Defendant's ANDA Product meets all of the elements of claim 1 of the '111 patent.

2. Conclusions of Law

As discussed above, I hold that Defendant failed to prove by clear and convincing evidence that claim 1 of the '111 patent is invalid as obvious. Defendant has made no other noninfringement arguments. Since Plaintiff has shown by a preponderance of evidence that Defendant's ANDA product meets all limitation of this claim, I hold that Defendant infringes claim 1 of the '111 patent.

D. Infringement of the '195 Patent

Plaintiff asserts that Defendant indirectly infringes claim 11 of the '195 patent. Prior to trial, the non-infringement arguments raised by Defendant as to the '195 patent were limited to (1) invalidity, (2) that Defendant did not administer any compounds, (3) no single entity performed all of the steps of the method, and (4) Defendant's product does not meet the claimed dissolution profile. (D.I. 129 at 4). By order dated May 19, 2017, I held that Defendant would not be allowed to raise new non-infringement arguments for the first time at trial and that Defendant had waived the right to contest the "sustained release" limitation of claim 11. (*Id.* at 3, 5).

1. Findings of Fact

1. As construed by the Court, the term "administering" as used in claim 11 of the '195 patent means "delivering into the body." (D.I. 62).
2. As construed by the Court, the preamble "having reduced adverse effects" in claim 11 of the '195 patent is not limiting. (D.I. 62).
3. Actavis had knowledge of the '195 patent prior to filing Actavis's ANDA. (D.I. 131, Ex. 1 at ¶18).
4. Claim 11 recites only one step—"administering" naltrexone or a pharmaceutically acceptable salt thereof and bupropion or a pharmaceutically acceptable salt thereof. (Tr. 159:15-160:1).
5. Claim 11 does not require a separate diagnosing step. (Tr. 160:2-160:14).
6. Because the patient will administer bupropion or a pharmaceutically acceptable salt thereof and

naltrexone or a pharmaceutically acceptable salt thereof to himself or herself, a single actor performs all of the steps of the method recited in claim 11 of the '195 patent. (*See* Tr. 158:10-12, 159:15-160:14).

7. The proposed labeling for Defendant's ANDA Product states that it is "indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial body mass index (BMI) of: 30 kg/m^2 or greater (obese) or 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbid condition (*e.g.,* hypertension, type 2 diabetes mellitus, or dyslipidemia)." (PTX-022.0001; D.I. 131, Ex. 1 at ¶59; Tr. 223:24-224:24).

8. The proposed labeling for Defendant's ANDA Product states that "Naltrexone hydrochloride and bupropion hydrochloride extended-release tablets should be taken by mouth in the morning and in the evening." (PTX-022.0006; Tr. 223:24-224:24).

9. The "Dosage and Administration" section of the proposed labeling for Defendant's ANDA Product sets forth the following titration schedule:

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

Naltrexone hydrochloride and bupropion hydrochloride extended-release tablets dosing should be escalated according to the following schedule:

	Morning Dose	**Evening Dose**
Week 1	1 tablet	None
Week 2	1 tablet	1 tablet
Week 3	2 tablets	1 tablet
Week 4 – Onward	2 tablets	2 tablets

A total daily dosage of two naltrexone hydrochloride and bupropion hydrochloride extended-release tablets 8 mg/90 mg tablets twice daily (32 mg/360 mg) is reached at the start of Week 4

(PTX-022.0006; D.I. 131, Ex. 1 at ¶ 62; Tr. 223:24-224:24).

10. At the end of the titration schedule, Defendant's proposed label instructs patients to take a total of 32 mg naltrexone hydrochloride and 360 mg bupropion hydrochloride per day. (*Id.*).

11. At the end of the titration schedule, Defendant's proposed label instructs patients to take two tablets of Defendant's ANDA Product per day in a "Morning Dose" and two tablets of Defendant's ANDA Product per day in an "Evening Dose," *i.e.* 16 mg naltrexone hydrochloride and 180 mg bupropion hydrochloride twice daily. (*Id.*).

12. Defendant's ANDA Product is a tablet containing sustained-release bupropion hydrochloride and sustained-release naltrexone hydrochloride. (Tr. 223:24-224:24, 226:13-18; D.I. 131, Ex. 1 at ¶ 60).

13. Defendant conducted dissolution testing on Lot # 2284R0007 of its ANDA Product, an exhibit batch used for its ANDA submission. (PTX-

019.0010; PTX-016.0179; D.I. 131, Ex. 1 at ¶ 61; Tr. 230:24-231:20).

14. Lot # 2284R0007 is representative of Defendant's ANDA Product. (*See* Tr. 255:12-19).

15. Defendant conducted dissolution testing using USP Apparatus 2 at 100 rpm in water at 37°C on six tablets from Lot # 2284R0007, the results of which are set forth below:

Table 4. Dissolution Profile (Naltrexone Hydrochloride) of Lot # 2284R0007 at 100 rpm, paddle [Water, USP Apparatus II, 900 mL]

Units	30 min	60 min	120 min	180 min	240 min	360 min	480 min	600 min
1	30	43	64	90	101	101	101	102
2	27	40	58	72	96	103	104	104
3	30	44	65	82	103	106	107	107
4	28	40	58	71	83	102	103	103
5	30	43	62	77	90	103	105	105
6	30	42	61	78	91	102	103	103
Mean	*29*	42	61	78	94	103	104	104
Min	27	40	58	71	83	101	101	102
Max	30	44	65	90	103	106	107	107
%RSD	4.2	4.0	5.1	8.7	7.8	1.7	1.8	1.7

(PTX-019.0011; PTX-015.0005; Tr. 232:5-233:13, 262:5-23, 264:7-15).

16. Claim 11 of the '195 patent does not require analysis or interpretation of the dissolution profile testing results as set forth on page 1943 of the United States Pharmacopeia. (Tr. 248:10-16).

17. Defendant's testing showed that its ANDA Product includes tablets that meet the dissolution profile for naltrexone recited in claim 11 of the '195 patent, *i.e.* between 39% and 70% of naltrexone released in one hour, between 62% and 90% of naltrexone released in two hours and at least

99% in 8 hours. (PTX-019.0011; Tr. 228:20-229:13).

18. Through its label (as set forth in D.I. 165 at ¶¶100-11), Defendant actively encourages patients to practice each element of the claimed method of claim 11 by administering Defendant's ANDA Product to themselves.

19. Plaintiff established by a preponderance of the evidence that each of the limitations of Claim 11 of the '195 patent are demonstrated by Defendant's ANDA, and that Defendant had the requisite intent to induce infringement, including knowledge of the '195 patent before submitting its ANDA. (PTX-015.0005; PTX-016.0179; PTX-019.0010-.0011; PTX-022.0001, .0006; D.I. 131, Ex. 1 at ¶¶ 18, 59-62; Tr. 158:10-12, 159:15-160:14, 221:22-234:11).

2. Conclusions of Law

Defendant's non-infringement arguments as to claim 11 of the '195 patent all center on whether its proposed ANDA product meets the claimed dissolution profile. For example, Defendant argues that Plaintiff "has adduced no evidence that Actavis knows what the dissolution profile of Actavis's ANDA Product will actually be in any given administration." (D.I. 165 at 70, ¶ 180). Specifically, Defendant argues that the dissolution profiles of some of the tablets it tested fall outside the claimed range of between 62% and 90% at two hours. (*Id.*, ¶ 181). Defendant also argues that a specific analysis or interpretation protocol is implicitly required by the claim as being part of the USP Apparatus 2 method. (*Id.* at 66-67, ¶¶ 159-67).

As an initial matter, I do not think the claim requires performing the separate analysis or interpretation protocol set forth in the United States Pharmacopeia ("USP"). Defendant argues that because the claim requires the dissolution profile to have certain characteristics when measured using USP Apparatus 2, the protocol for interpretation of the data obtained using the method must also be used. (D.I. 165 at 66-69, ¶¶ 158-77; Tr. 243:11-248:20). I am not persuaded. The claim specifies that the dissolution profile must be measured using USP Apparatus 2. There is no mention of interpretation or analysis in the claim language. Plaintiff's expert, Dr. Treacy, credibly testified that a person of ordinary skill would not have read the claim to require the use of the additional analysis or interpretation protocol "specified in general Chapter 711 of the USP." (Tr. 248:10-16). Defendant did not present expert testimony in rebuttal of Dr. Treacy's conclusion. Defendant cannot create a dispute of fact on an issue requiring technical analysis based solely on attorney argument. *Invitrogen Corp. v. Clontech Labs., Inc.,* 429 F.3d 1052, 1068 (Fed. Cir. 2005).

While it is certainly true that some of the tablets fall slightly outside of the claimed range for the two hour dissolution data, I disagree that this has any relevance to the question of whether Defendant's product infringes. Defendant does not appear to dispute that some of the tablets it tested fall squarely within the claimed dissolution profile; rather, Defendant suggests that in order to prevail on its infringement claim, Plaintiff must prove that Defendant knows of some particular administration of the ANDA product that will meet the claimed dissolution profile. (*Id.* at

69-70, ¶¶179-182). This is not the law. "[A]an accused product that sometimes, but not always, embodies a claimed method nonetheless infringes." *Bell Commc'ns Research, Inc. v. Vitalink Commc'ns Corp.,* 55 F.3d 615, 622-23 (Fed. Cir. 1995). Plaintiff has adduced sufficient evidence to prove by a preponderance of the evidence that at least some of Defendant's tablets will meet the claimed dissolution profile. This is all that is required for a finding of infringement.

Defendant also argues that Plaintiff cannot prove that it "specifically intends to encourage infringement" because its "proposed label does not even mention the dissolution profile" of its product. (D.I. 165 at 70, ¶¶ 183-85). I have already concluded that Defendant's proposed ANDA product meets the dissolution profile; I do not think it is necessary for infringement of this method claim to find that Defendant's proposed label includes the dissolution profile. The claimed method requires administering a product with specific properties. Defendant's product meets all limitations in the claim and the label instructs on administering the product in the amount and with the frequency recited in the claim. Whether the patient who performs the method by administering the tablets knows that the tablets meet the dissolution profile is irrelevant for the purposes of infringement. Defendant knows that the tablets meet all of the claim limitations and, through its proposed label, encourages patients to administer the tablets in a manner that infringes the claimed method.

For the foregoing reasons, I hold that Plaintiff has proven by a preponderance of the evidence that Defendant induces infringement of claim 11 of the '195 patent.

E. Infringement of the '626 Patent

Plaintiff asserts that Defendant indirectly infringes claims 2, 15, 26, and 31 of the '626 patent. As discussed above, I think the question of infringement of claims 2 and 15 is moot. Prior to trial, the non-infringement arguments raised by Defendant as to the '626 patent were limited to (1) invalidity, (2) that Defendant did not administer any compounds, (3) no single entity performed all of the steps of the method, and (4) the proposed label did not include instructions to administer naltrexone and bupropion "to increase satiety" or "suppress the appetite." (D.I. 129 at 3-4). By order dated May 19, 2017, I held that Defendant would not be allowed to raise new non-infringement arguments for the first time at trial and had waived the right to contest the "effective to induce weight loss" and "effective to enhance the weight loss effect" limitations of the asserted claims. (*Id.* at 3, 5).

1. Findings of Fact

1. As construed by the Court, the term "administering" as used in the claims of the '626 patent means "delivering into the body." (D.I. 62).
2. As construed by the Court, the term "a weight loss effective amount of a first and second compound" as used in the claims of the '626 patent means "a weight loss effective amount of a first and second compound, in combination." (D.I. 62).
3. Actavis had knowledge of the '626 patent prior to filing Actavis's ANDA. (D.I. 131, Ex. 1 at ¶ 18)
4. Actavis's ANDA sets forth a method for treating overweight or obesity through the use of Actavis's

ANDA Product. (D.I. 131, Ex. 1 at ¶ 19; PTX-022; Tr. 87:11-88:2).

5. Actavis's ANDA instructs physicians (or other healthcare provider) to diagnose an individual as suffering from overweight or obesity by determining that the individual has a body mass index ("BMI") of at least 27 kg/m^2. (PTX-022.0001, 0005-.0007; Tr. 87:20-88:2).

6. Actavis's ANDA (prescribing information) includes a BMI conversion chart for use in diagnosis. (PTX-022.0007; Tr. 87:21-88:2).

7. Actavis's ANDA Product is indicated for the treatment of obese or overweight individuals based on calculating BMI. (PTX-022.0001, 0005-.0007; Tr. 87:11-88:2, 92:15-93:8).

8. Each tablet of Defendant's ANDA Product contains 90 mg of bupropion HC1 and 8 mg naltrexone HC1 in a single extended-release, oral dosage form. (D.I. 131, Ex. 1 at ¶¶ 33-34; Tr. 91:13-92:14, 93:8-10, 95:4-13, 98:14-23).

9. As Defendant's ANDA Product contains both bupropion and naltrexone in a single tablet, the two active ingredients are administered together when a patient takes the product. (PTX-022.0002, .0006, .0008; Tr. 91:13-23, 95:4-13).

10. As required by claims 26 and 31, the amount of bupropion and naltrexone in combination in Defendant's ANDA Product is effective to cause weight loss for an overweight or obese individual. (PTX-022.0005-.0006, .0039-.0040; Tr. 92:18-93:10, 152:23-153:3).

11. As required by claims 26 and 31, the weight loss activity of the bupropion and naltrexone in Defendant's ANDA Product is enhanced compared to the administration of the same amount of naltrexone or bupropion alone. (PTX-022.0005, .0028, .0039-0040; Tr. 90:7-91:8, 92:15-93:8, 93:11-19, 94:10-23, 114:11-24, 152:23-153:3).

12. Claim 25 of the '626 patent, from which claims 26 and 31 depend, only contains an administering step. (JTX-002.0024; Tr. 85:1-7, 158:13-159:3).

13. Through its label, Defendant actively encourages patients to practice each element of the claimed method of claim 26 by administering Defendant's ANDA Product to themselves in accordance with the limitations of claim 26.

14. Through its label (as set forth in D.I. 165 at ¶¶ 8-71), Defendant actively encourages patients to practice each element of the claimed method of claim 31 by administering Defendant's ANDA Product to themselves in accordance with the limitations of claim 31.

15. Plaintiff established by a preponderance of the evidence that each of the limitations of Claims 26 and 31 of the '626 patent is demonstrated by Defendant's ANDA, and that Defendant had the requisite intent to induce infringement, including knowledge of the '626 patent before submitting its ANDA. (D.I. 131, Ex. 1 at ¶¶ 18-19, 33-34; PTX-022.0001-.0003, 0005-.0006, .0028, .0039-0040; Tr. 77:6-96:14, 152:23-153:3; 157:18-183:8).

2. Conclusions of Law

As summarized in the findings of fact above, at trial, Plaintiff presented evidence that Defendant's proposed label induces infringement by meeting all limitations of claims 26 and 31 of the '626 patent. Divided infringement was the only non-infringement defense Defendant presented at trial. (D.I. 165 at 40, ¶ 83). I have already held that claims 26 and 31 involve the single step of administering and do not require a separate diagnosing step. Therefore, I hold that Plaintiff has shown by a preponderance of evidence that Defendant's ANDA product infringes claims 26 and 31 of the '626 patent.

V. CONCLUSION

Defendants failed to prove by clear and convincing evidence that claims 26 and 31 of the '626 patent, claim 1 of the '111 patent, and claim 11 of the '195 patent are invalid. Plaintiff proved by a preponderance of the evidence that Defendant directly infringes claim 1 of the '111 patent and indirectly infringes claims 26 and 31 of the '626 patent and claim 11 of the '195 patent.

Plaintiffs should submit an agreed upon form of final judgment within two weeks.

APPENDIX C

NOTE: This order is nonprecedential.

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

NALPROPION PHARMACEUTICALS, INC.,
Plaintiff-Appellee

v.

ACTAVIS LABORATORIES FL, INC.,
Defendant-Appellant

2018-1221

Appeal from the United States District Court for the District of Delaware in No. 1:15-cv-00451-RGA, Judge Richard G. Andrews.

ON PETITION FOR PANEL REHEARING AND REHEARING EN BANC

Before Prost, *Chief Judge,* NEWMAN, LOURIE, DYK, MOORE, O'MALLEY, REYNA, WALLACH, TARANTO, CHEN, HUGHES, AND STOLL, *Circuit Judges.*

PER CURIAM.

ORDER

Appellant Actavis Laboratories FL, Inc. filed a combined petition for panel rehearing and rehearing en banc. A response to the petition was invited by the court and filed by Appellee Nalpropion Pharmaceuticals LLC. The petition was referred to the panel that heard the appeal, and thereafter the petition for rehearing en banc was referred to the circuit judges who are in regular active service.

Upon consideration thereof,

IT IS ORDERED THAT:

The petition for panel rehearing is denied.

The petition for rehearing en banc is denied.

The mandate of the court will issue on December 23, 2019.

FOR THE COURT

December 16, 2019
Date

/s/ Peter R. Marksteiner
Peter R. Marksteiner
Clerk of Court

APPENDIX D

United States Patent
McKinney et al.

Patent No.: US 8,916,195 B2
Date of Patent: Dec. 23, 2014

SUSTAINED RELEASE FORMULATION OF NALTREXONE

Inventors: **Anthony A. McKinney**, San Diego, CA (US); **Gary D. Tollefson**, Indianapolis, IN (US); **Richard Soltero**, Holly Springs, NC (US); **Thea Elise Dunzo**, Durham, NC (US)

Assignee: **Orexigen Therapeutics, Inc**., La Jolla, CA (US)

Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 974 days.

Appl. No.: **11/757,773**

Filed: **Jun. 4, 2007**

* * *

ABSTRACT

A sustained-release oral dosage form of naltrexone or a pharmaceutically acceptable salt thereof is provided. The oral dosage form may be administered with another compound. Administration of the oral dosage form may reduce a side effect, which may be a side effect at least partially attributable to a weight-loss treatment. The oral dosage form may be administered to treat a weight-loss condition.

* * *

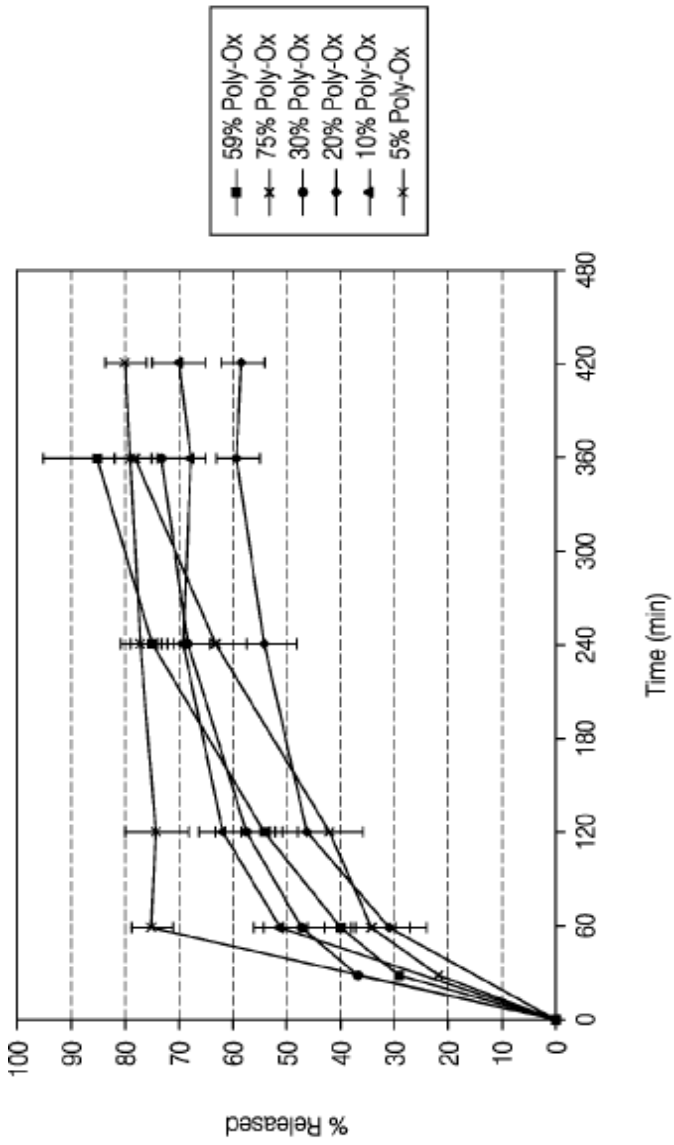
59% Poly-Ox
75% Poly-Ox
30% Poly-Ox
20% Poly-Ox
10% Poly-Ox
5% Poly-Ox
% Released
Time (min)
0
10
20
30
40
50
60
70
80
90
100
0
60
120
180
240
300
360
420
480

FIG. 1

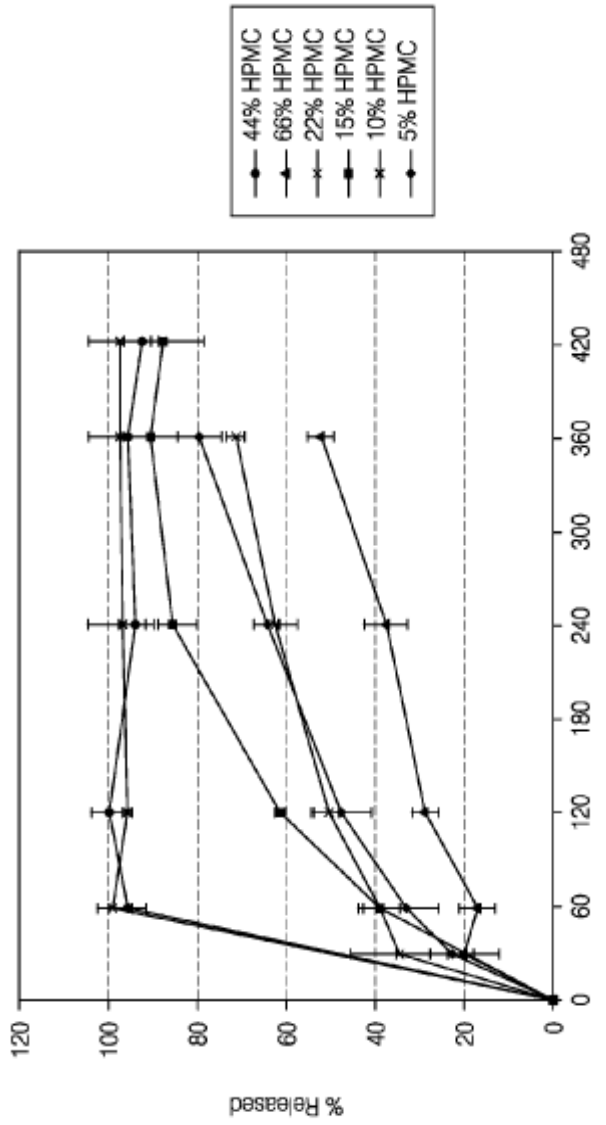
44% HPMC
66% HPMC
22% HPMC
15% HPMC
10% HPMC
5% HPMC
% Released
Time (min)
0
20
40
60
80
100
120
0
60
120
180
240
300
360
420
480

FIG. 2

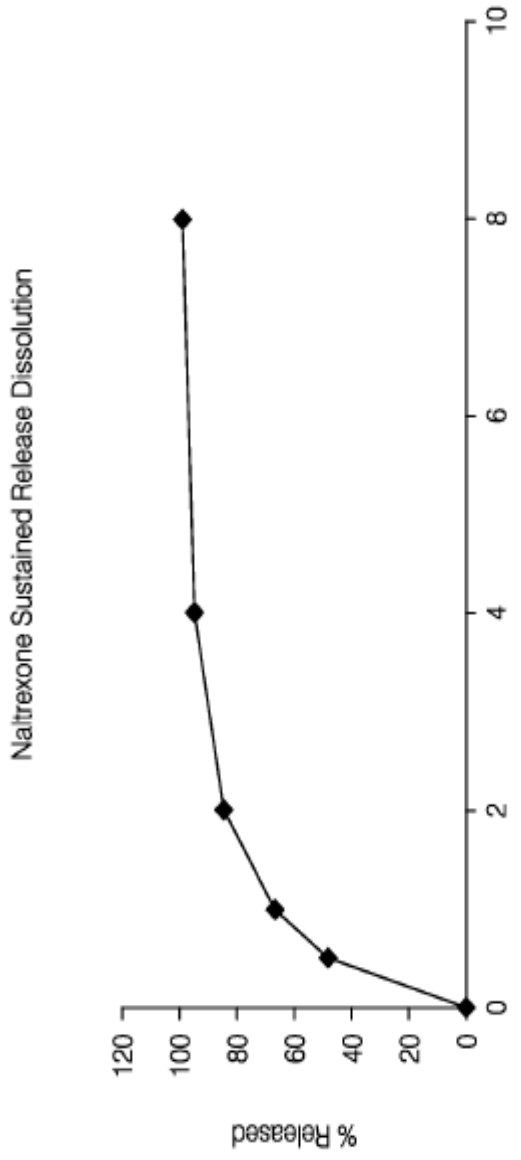
Naltrexone Sustained Release Dissolution
% Released
120
100
80
60
40
20
0
0
2
4
6
8
10
Time (hours)

FIG. 3

* * *

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** shows the dissolution profile of sustained release 5 mg naltrexone tablets containing polyethylene oxide.

FIG. **2** shows the dissolution profile of sustained release 5 mg naltrexone tablets containing hydroxypropylmethyl cellulose.

FIG. **3** shows the dissolution profile of sustained release naltrexone and bupropion tablets containing hydroxypropyl methyl cellulose.

* * *

DEFINITIONS

* * *

The term "release rate", as used herein, has its ordinary meaning as understood by those skilled in the art and thus includes, by way of non-limiting example, a characteristic related to the amount of an active ingredient released per unit time as defined by in vitro or in vivo testing. An in vitro release rate is determined by a "standard dissolution test.," conducted according to United States Pharmacopeia 24th edition (2000) (USP 24), pp. 1941-1943, using Apparatus 2 described therein at a spindle rotation speed of 100 rpm and a dissolution medium of water, at 37° C., or other test conditions substantially equivalent thereto.

* * *

Formulations

Oral dosage forms may comprise naltrexone and a sustained-release carrier. A sustained release carrier includes, by that are included in a pharmaceutical

formulation in amounts that are effective to extend the release rate of naltrexone from the formulation as compared to an immediate-release formulation (e.g., REVIA™ immediate-release naltrexone hydrochloride). A sustained release carrier may be referred to herein as a retardant excipient. Examples of sustained release carriers include hydroxypropylmethyl cellulose, polyethylene oxide, polyacrylate, copolymer of acrylate and methacrylate, methacrylate polymer, copolymer of acrylate and methacrylate, copolymer of acrylate and methacrylate with ammonium group, copolymer of maleic anhydride and methyl vinyl ether, hydroxy propyl ethyl cellulose, hydroxy propyl cellulose, hydroxy ethyl cellulose, methyl cellulose, hydroxymethyl methacrylate, maltodextrin, natural gum and xanthan gum. In some embodiments, the sustained-release carrier composition comprises at least one of hydroxypropylmethylcellulose and polyoxyethylene. A sustained release carrier composition may contain one or more sustained release carriers, along with other suitable ingredients.

In some embodiments, an oral dosage form comprising naltrexone comprises an amount of a sustained-release carrier composition that is effective to render the dosage form pharmacokinetically distinct from an immediate-release formulation (e.g., REVIA™ immediate-release naltrexone hydrochloride). For example, relative to the immediate-release formulation, the amount and type of sustained-release carrier composition may be selected to reduce the naltrexone C_{max} and/or the 6-beta naltrexol C_{max} (e.g., to about 80% or less than the naltrexone C_{max} of or 6-beta naltrexol C_{max} of immediate-release naltrexone).

The amount of the sustained-release carrier composition may be effective to provide an in vitro release rate of the naltrexone of less than about 90%, or less than about 80%, in about 2 hours. The amount of the sustained-release carrier composition may be effective to provide an in vitro release rate of the naltrexone of less than about 98% in about 4 hours. The amount of the sustained-release carrier composition maybe effective to provide an invitro release rate of the naltrexone of less than about 80% or than about 70% in about 1 hour. In vitro release rate is determined by a standard dissolution test as described above.

A description of representative sustained release carrier materials can be found in the Remington: The Science and Practice of Pharmacy (20th ed, Lippincott Williams & Wilkens Publishers (2003)), which is incorporated herein by reference in its entirety. Those skilled in the art can formulate sustained-release carrier compositions using routine experimentation informed by the detailed guidance provided herein.

Dosage forms described herein may be formulated to comprise various excipients, binders, carriers, disintegrants, coatings, etc. Pharmaceutical preparations can be obtained by mixing one or more solid excipients with a pharmaceutical composition as described herein, optionally grinding the resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain pharmaceutical compositions suitable for use in various forms, e.g., as pills, tablets, powders, granules, dragees, capsules, liquids, sprays, gels, syrups, slurries, suspensions and the like, in bulk or unit dosage forms, for oral ingestion by a patient to be treated. Various examples of unit dosage forms are described herein;

non-limiting examples include a pill, a tablet, a capsule, a gel cap, and the like. Examples of suitable excipients are listed below, some of which are mentioned above as having particular dissolution properties. Pharmaceutically acceptable carriers or diluents for therapeutic use are well known in the pharmaceutical art, and are described, for example, in Remington: The Science and Practice of Pharmacy (2003), which is hereby incorporated by reference in its entirety. The term "carrier" material or "excipient" herein can mean any substance, not itself a therapeutic agent, used as a carrier, diluent, adjuvant, binder, and/or vehicle for delivery of a therapeutic agent to a subject or added to a pharmaceutical composition to improve its handling or storage properties or to permit or facilitate formation of a dose unit of the composition into a discrete article such as a capsule or tablet suitable for oral administration. Excipients can include, by way of illustration and not limitation, diluents, disintegrants, binding agents, adhesives, wetting agents, polymers, lubricants, glidants, substances added to mask or counteract a disagreeable taste or odor, flavors, dyes, fragrances, and substances added to improve appearance of the composition. The glidants may be one or more of colloidal silicon dioxide, talc, corn starch, DL-leucine, sodium lauryl sulfate, and magnesium, calcium and sodium stearates. The diluents may be one or more of lactose, starch, mannitol, sorbitol, dextrose, microcrystalline cellulose, dibasic calcium phosphate, sucrose based diluents, confectioners sugar, monobasic calcium sulfate monohydrate, calcium sulfate dihydrate, calcium lactate trihydrate, dextrates, inositol, hydrolyzed cereal solids, amylose, powdered cellulose, calcium carbonate, glycine, or bentonite.

Acceptable excipients include lactose, sucrose, starch powder, maize starch or derivatives thereof, cellulose esters of alkanoic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, saline, dextrose, mannitol, lactose, lecithin, albumin, sodium glutamate, cysteine hydrochloride, and the like. Examples of suitable excipients for soft gelatin capsules include vegetable oils, waxes, fats, semisolid and liquid polyols. Suitable excipients for the preparation of solutions and syrups include, without limitation, water, polyols, sucrose, invert sugar and glucose. The pharmaceutical compositions can additionally include preservatives, solubilizers, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorings, buffers, coating agents, or antioxidants. Dissolution or suspension of the active ingredient in a vehicle such as water or naturally occurring vegetable oil like sesame, peanut, or cottonseed oil or a synthetic fatty vehicle like ethyl oleate or the like may be desired. Buffers, preservatives, antioxidants and the like can be incorporated according to accepted pharmaceutical practice. The compound can also be made in microencapsulated form. If desired, absorption enhancing preparations (for example, liposomes), can be utilized. Those skilled in the art can formulate sustained-release dosage forms containing one or more of the foregoing ingredients by routine experimentation informed by the detailed guidance provided herein.

* * *

EXAMPLES

* * *

The following example describes the dissolution profiles of the sustained release naltrexone formulations described above.

Example 2

The dissolution measurements for the tablets were completed using a 10-mesh baskets at 100 rpm. Samples were analyzed using a UV-VIS at λ_{max} of 280. The dissolution data of the active pharmaceutical ingredient (API) for the HPMC formulations and PolyOx formulations are presented in Tables 5 and 6, respectively. Dissolution data for the HPMC formulations and PolyOx formulations are also plotted in FIGS. **1** and **2**, respectively.

TABLE 5

Dissolution Data for HPMC Formulations

Time (min)	% API Released 5% HPMC	Std. Dev. 5% HPMC	% API Released 10% HPMC	Std. Dev. 10% HPMC	% API Released 15% HPMC	Std. Dev. 15% HPMC	% API Released 22% HPMC	Std. Dev. 22% HPMC	% API Released 44% HPMC	Std. Dev. 44% HPMC	% API Released 66% HPMC	Std. Dev. 66% HPMC
0	0	0	0	0	0	0	0	0	0	0	0	0
30							35	11	23	5	20	8
60	96	4	99	4	39	5	39	4	33	7	17	4
120	100	4	96	1	62	1	51	3	48	7	29	3
240	94	4	97	8	86	6	63	5	65	3	38	5
360	96	0	98	7	91	6	72	2	80	5	53	3
420	93	4	98	7	88	9						

TABLE 6

Dissolution Data for Polyethylene Oxide Formulations

Time (min)	% API Released 5% PolyOx	Std. Dev. 5% PolyOx	% API Released 10% PolyOx	Std. Dev. 10% PolyOx	% API Released 20% PolyOx	Std. Dev. 20% PolyOx	% API Released 30% PolyOx	Std. Dev. 30% PolyOx	% API Released 59.3% PolyOx	Std. Dev. 59.3% PolyOx	% API Released 75% PolyOx	Std. Dev. 75% PolyOx
0	0	0	0	0	0	0	0	0	0	0	0	0
30							37	13	29	1	22	12
60	75	7	51	5	31	7	47	6	40	3	34	24
120	74	6	62	4	46	6	57	3	54	1	42	15
240	77	4	69	5	54	6	68	5	75	4	63	17
360	79	6	68	3	59	4	73	10	85	10	78	13
420	80	4	70	5	58	4						

Example 3

Sustained-release naltrexone-bupropion tri-layer tablets were made using the ingredients listed in Table 7 through Table 9, in accordance with the general methods for making tri-layer tablets described in U.S. Provisional Patent Application Ser. No. 60/865,157, filed Nov. 9, 2006, which is hereby incorporated by reference in its entirety. A sustained-release naltrexone formulation was made by combining the following components:

TABLE 7

Naltrexone Blend Formulation

Component	mg/tablet	mass (g)
Naltrexone Hydrochloride	13.22	1983.0
Edetate Disodium, USP	0.23	34.5
Hydroxypropylmethylcellulose (Methocel K15 Premium CR)	22.50	3375.0
Hydroxypropylcellulose	11.00	1650.0
Lactose Monohydrate NF, Fast Flo 316	45.50	6825.0
Microcrystalline cellulose (Avicel PH102)	128.95	19342.5
Colloidal silicon dioxide, NF	2.30	345.0
Magnesium Stearate, NF	1.30	195.0
Total	225.0	33750.0

Thus, the sustained-release naltrexone formulation includes 10% HPMC. A bupropion blend was made by combining the following components:

TABLE 8

Bupropion Blend Formulation

Component	mg/tablet	mass (g)
Bupropion Hydrochloride Granulation	315.00	47250.0
Magnesium Stearate	2.00	300.0
Total	317.00	47550.0

An inert layer blend was made by combining the following components:

TABLE 9

Inert Blend Formulation

Component	mg/tablet	mass (g)
Anhydrous Lactose	30.00	4500.0
Microcrystalline cellulose (Avicel PH101)	84.70	12705.0
Crospovidone	3.60	540.0
Magnesium Stearate	1.20	180.0
FDC Blue #2 Aluminum Lake	0.50	75.0
Total	120.0	18000.0

The sustained-release naltrexone formulation, bupropion blend and inert layer blends were used to form 150 tri-layer tablets with the naltrexone and bupropion layers on opposite sides of the inert layer, such that each tablet was 662.00 mg. The tablets each contained 11.94 mg of naltrexone (13.22 mg naltrexone hydrochloride).

The dissolution data of naltrexone for the tablets is presented in Table 10. Dissolution data is also plotted in FIG. **3**.

TABLE 10

Dissolution Data for Naltrexone-Bupropion Tablets

Time (Hours)	Naltrexone Released (Wt %)
0	0
0.5	48
1	67
2	85
4	95
8	99

* * *

What is claimed is:

1. A method of treating overweight or obesity having reduced adverse effects comprising:

identifying a subject in need of a treatment for obesity or overweight; and

orally administering at least daily about 4 mg to about 32 mg of naltrexone and about 90 mg to about 360 mg of bupropion, or pharmaceutically acceptable salts thereof to said subject, wherein the bupropion or pharmaceutically acceptable salt thereof is administered as a sustained-release formulation, wherein the naltrexone or pharmaceutically acceptable salt thereof is administered as a sustained-release formulation having an in vitro naltrexone dissolution profile in a dissolution test of USP Apparatus 2 Paddle Method at 100 rpm in a dissolution medium of water at 37° C. of:

a) between 39% and 70% of naltrexone released in one hour, and

b) between 62% and 90% of naltrexone released in two hours,

whereby at least one adverse effect associated with administration of the same amount of an immediate release naltrexone formulation and said sustained release formulation of bupropion or a pharmaceutically acceptable salt thereof is reduced.

2. The method of claim **1**, wherein the amount of bupropion or pharmaceutically acceptable salt thereof administered per day is selected from the group consisting of about 90 mg, about 180 mg, about 270 mg, and about 360 mg, and the amount of naltrexone or pharmaceutically acceptable salt thereof administered per day is selected from the group consisting of about 4 mg, about 8 mg, about 12 mg, about 16 mg, about 24 mg and about 36 mg.

3. The method of claim **2**, wherein said naltrexone and bupropion, or pharmaceutically acceptable salts thereof, are administered in a single oral unit dosage form.

4. The method of claim **2**, wherein said sustained-release formulation of naltrexone provides an in vivo plasma concentration profile of:

a) a naltrexone C_{max} that is less than 80% of the naltrexone C_{max} of an equal amount of immediate-release naltrexone hydrochloride; and

b) a naltrexone AUC_{last} that is between 80% and 125% of the naltrexone AUC_{last} of an equal amount of immediate-release naltrexone hydrochloride.

5. The method of claim **4**, wherein said naltrexone and bupropion, or pharmaceutically acceptable salts thereof, are administered in a single oral unit dosage form.

6. The method of claim **1**, wherein said sustained-release formulation of naltrexone or a pharmaceutically acceptable salt thereof provides an in vitro release rate of naltrexone in the dissolution test of at least 99% in 8 hours.

7. The method of claim **1**, wherein said sustained-release formulation of naltrexone or a pharmaceutically acceptable salt thereof is administered twice daily.

8. The method of claim **1**, wherein said sustained-release formulation of naltrexone or a pharmaceutically acceptable salt thereof provides an in vitro release rate of naltrexone in the dissolution test of between 23% to 48% in 0.5 hour, between 51% and 67% in 1 hour, and between 74% and 90% in 2 hours.

9. The method of claim **8**, wherein said in vitro release rate of naltrexone is about 85% in 2 hours.

10. The method of claim **9**, wherein said sustained-release formulation of naltrexone or a pharmaceutically acceptable salt thereof provides an in vitro release rate of naltrexone in the dissolution test of at least 99% in 8 hours.

11. A method of treating overweight or obesity having reduced adverse effects comprising orally administering daily about 32 mg of naltrexone and about 360 mg of bupropion, or pharmaceutically acceptable salts thereof, to a person in need thereof, wherein the bupropion or pharmaceutically acceptable salt thereof is

administered as a sustained-release formulation, wherein the naltrexone or pharmaceutically acceptable salt thereof is administered as a sustained-release formulation, and wherein said sustained-release formulation of naltrexone has an in vitro naltrexone dissolution profile in a dissolution test of USP Apparatus 2 Paddle Method at 100 rpm in a dissolution medium of water at 37° C. of:

a) between 39% and 70% of naltrexone released in one hour,

b) between 62% and 90% of naltrexone released in two hours; and

c) at least 99% in 8 hours;

wherein about 16 mg of said sustained-release formulation of naltrexone or a pharmaceutically acceptable salt thereof is administered twice daily, and about 180 mg of said sustained-release formulation of bupropion or a pharmaceutically acceptable salt thereof is administered twice daily.

12. The method of claim **1**, wherein said at least one adverse effect comprises at least one adverse effect selected from the group consisting of nausea, headache and dizziness.

13. The method of claim **12**, wherein said at least one adverse effect comprises nausea.

14. The method of claim **1**, wherein said sustained-release naltrexone formulation or pharmaceutically acceptable salt thereof and said sustained-release bupropion or pharmaceutically acceptable salt thereof are administered in separate oral dosage forms.

15. The method of claim **4**, wherein said sustained-release formulation of naltrexone further provides an in vivo plasma concentration profile of:

c) a 6-beta naltrexol C_{max}, that is less than 80% of the 6-beta naltrexol C_{max} of an equal amount of immediate-release naltrexone hydrochloride; and

d) a 6-beta naltrexol AUC_{last} that is between 80% and 125% of the 6-beta naltrexol AUC_{last} of an equal amount of immediate-release naltrexone hydrochloride.