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, Venable 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

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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 11 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.

amount effective to enhance the weight loss activity of bupropion. '626 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 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.

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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").

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 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–

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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").

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

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 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

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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).

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 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.

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[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).

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 re-leased in one hour;
> b) between 62% and 90% of naltrexone re-leased 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 ("PolyOx"), 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 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

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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] . . . .'").

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.