No. 18-1221

**IN THE UNITED STATES COURT OF APPEALS**
**FOR THE FEDERAL CIRCUIT**

NALPROPION PHARMACEUTICALS, INC.,

*Plaintiff-Appellee,*

v.

ACTAVIS LABORATORIES FL, INC.,

*Defendant-Appellant.*

On Appeal from the United States District Court
for the District of Delaware
Civil Action No. 15-00451, Judge Richard G. Andrews

# PETITION FOR REHEARING AND REHEARING EN BANC BY ACTAVIS LABORATORIES FL, INC.

Scott J. Bornstein
Jonathan D. Ball, Ph.D.
Richard C. Pettus
Justin A. MacLean
MetLife Building
200 Park Avenue
GREENBERG TRAURIG LLP
New York, NY 10166
Tel.: (212) 801-9200

William M. Jay
Jaime A. Santos
GOODWIN PROCTER LLP
901 New York Avenue, N.W.
Washington, DC 20001
Tel.: (202) 346-4000

Alexandra D. Valenti
GOODWIN PROCTER LLP
620 Eighth Avenue
New York, NY 10018
Tel.: (212) 813-8800

*Attorneys for Defendant-Appellant Actavis Laboratories FL, Inc.*

October 16, 2019

# CERTIFICATE OF INTEREST

Counsel for Appellant Actavis Laboratories FL, Inc., William M. Jay, certifies the following:

1. The full name of every party or amicus represented by me is:

Actavis Laboratories FL, Inc.

2. The name of the real party in interest (if the party named in the caption is not the real party in interest) represented by me is:

N/A

3. All parent corporations and any publicly held companies that own 10 percent or more of the stock of the party or amicus curiae represented by me are:

Teva Pharmaceuticals USA, Inc.; Teva Pharmaceutical Industries Ltd.

4. The names of all law firms and the partners or associates that appeared for the party or amicus now represented by me in the trial court or agency and are not expected to appear in this Court are:

Young, Conaway, Stargatt & Taylor LLP: James L. Higgins, Melanie K. Sharp, Monte Terrell Squire, Robert M. Vrana; Willkie Farr & Gallagher LLP: Dan Constantinescu, Thomas J. Meloro

5. The title and number of any case known to counsel to be pending in this or any other court or agency that will directly affect or be directly affected by this Court's decision in the pending appeal.

None.

/s/ William M. Jay
William M. Jay
Goodwin Procter LLP
901 New York Avenue NW
Washington, DC 20001
Tel.: 202.346.4000

*Counsel for Appellant Actavis Laboratories FL, Inc.*

Dated: October 16, 2019

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## RULE 35(b) STATEMENT

Based on my professional judgment, I believe the panel decision is contrary to the following precedents of this Court: *Ariad Pharmaceuticals, Inc. v. Eli Lilly & Co.*, 598 F.3d 1336 (Fed. Cir. 2010) (en banc), *Lucent Technologies, Inc. v. Gateway, Inc.*, 543 F.3d 710 (Fed. Cir. 2008), *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565 (Fed. Cir. 1997), and *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555 (Fed. Cir. 1991).

Based on my professional judgment, I believe this appeal requires an answer to a precedent-setting question of exceptional importance: To comply with the written-description requirement, must the specification describe "*the invention*, with all its claimed limitations," not just "that which makes it obvious," as this Court has long held? *E.g.*, *Lockwood*, 107 F.3d at 1572. Or for some claim limitations, can the specification merely disclose a "substantially equivalent" method step, as the panel majority concluded here?

/s/ William M. Jay
*Attorney of Record for Appellant*

## INTRODUCTION

This Court has long held that to comply with the written-description requirement of 35 U.S.C. § 112, "all the limitations must appear in the specification." *Lockwood v. Am. Airlines, Inc.*, 107 F.3d 1565, 1572 (Fed. Cir. 1997). A patentee cannot claim even an "obvious variant of that which is disclosed in the specification," *id.*, because "[w]hat is claimed by the patent application must be *the same as* what is disclosed in the specification," *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1347 (Fed. Cir. 2010) (en banc) (emphasis added) (quoting *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co. Ltd.*, 535 U.S. 722, 736 (2002)).

The panel majority held that "[w]hile as a general matter" the specification must disclose exactly what is claimed, it would make a new exception to that longstanding rule: for an amorphous set of claim limitations that a court deems less important, the written-description requirement is satisfied as long as what is disclosed in the specification is "substantially equivalent" to what is claimed. Op. 10, 12. As Chief Judge Prost recognized in dissent, this "new rule" conflicts with this Court's precedents. Dissent 1.

With this decision, different rules apply to different claim limitations even though every claim limitation is supposed to be equally material. Nothing in this Court's precedents supports creating different tiers of claim limitations depending

on whether a court believes a particular limitation to be major or minor. Nor does the text of Section 112 apply the written-description requirement more weakly to some limitations than to others. Yet the majority has replaced what was a bright-line rule with a "flexible" test, Op. 12, without even providing guidance about which types of claim limitations will be held to the more demanding standard set forth in *Ariad* and *Lockwood*, and which will be held to the diluted "substantially equivalent" rule established here. The full Court should take up this important issue and restore uniformity to this Court's precedents.

## BACKGROUND

This petition involves the last remaining impediment to generic competition for Contrave, a drug used for weight management in overweight or obese adults. The panel's decision allows one remaining claim of one remaining patent to block generic competition through 2030—even though the active ingredients, their combination, and their use have all been known for years. That last remaining claim is based on a specific dissolution profile—one never discussed in the patent's written description.

1. Claim 11 of U.S. Patent No. 8,916,195 claims a method of treating overweight or obesity using a sustained-release formulation of bupropion and naltrexone. Appx195(31:5-32:3). Claim 11 requires, among other limitations, that the formulation have a certain in vitro dissolution profile, which is measured at

specified intervals using "a dissolution test of USP Apparatus 2 Paddle Method." Op. 4-5; Appx195(31:5-32:3); Appx11322. In the USP 2 method, a tablet is placed in a container of water and a paddle is used to move the water over the surface of the tablet, releasing the drug from the tablet while it remains on the bottom of the container. Appx11315; Appx11349-11350.

Another method of measuring dissolution profile, known as the "USP 1" method, involves a different apparatus. In USP 1, the tablet is placed in a basket suspended in the middle of the water in the container; the basket rotates in the water and releases drug from the tablet. Appx11315; Appx11349. Thus, USP 2 moves the water around the tablet, and USP 1 moves the tablet through the water.[1]

Because of the different flow dynamics in the two apparatuses, the two methods will result in different dissolution profiles for the same formulation. Indeed, the named inventor of the '195 patent testified that the two methods are not "comparable" and that when he tested the claimed formulation, he obtained different results for the in vitro dissolution of naltrexone using the two methods. Appx11319-11321; *see also* Appx11350; Appx11356-11358.

While claim 11 unambiguously requires a dissolution profile measured using USP 2, the specification of the '195 patent does not disclose a sustained-release

[1] *See* https://www.youtube.com/watch?v=tHqPkAYp17E demonstrating the different methods.

formulation with a dissolution profile matching claim 11 and measured using USP 2. The district court and panel majority focused on Examples 2 and 3 of the specification, which report dissolution testing data at specified timepoints. Op. 8-9; Appx188-189. Example 2, in which the district court found disclosure of the lower bounds of the one- and two-hour ranges required by claim 11, undisputedly provides dissolution data obtained *using USP 1*. Op. 8-9; Appx188(18:27) ("10-mesh baskets"); *see* Appx11322; Appx11366-11367; Appx11416. Example 3 is silent about whether the data were obtained using USP 1 or USP 2. Op. 9; Appx189(19:3-10).

2. Claim 11's requirement that the sustained-release formulation have a specific dissolution profile measured using USP 2 was critical to the issuance of the '195 patent. Dissent 3-4. During prosecution, the claims were repeatedly rejected over the Weber reference, Appx3751, Appx3755-3757; Appx3784-3793; Appx3835, Appx3838-3847; Appx3875-3886, and the examiner suggested that the applicants "define the formulation and/or patient population" to overcome the rejection. Appx3897. The applicants proposed a new claim that recited a "standard dissolution test," rather than USP 2, but was otherwise identical to the later-issued claim 11. Appx3976-3977 (claim 79). The claim was again rejected. Appx6987, Appx6994-6998. The applicants then amended the claim to require that the dissolution profile be measured using USP 2. Appx7034-7035 (claim 79).

They argued that adding "the specific dissolution test conditions" overcame Weber. Appx7039.

This time the examiner allowed the claim, expressly referring to the addition of USP 2 as a reason for allowance:

> [Weber's] teachings … do not direct one to obtain the claimed method with a sustained-release formulation of naltrexone or pharmaceutically acceptable salt thereof having an in vitro naltrexone dissolution profile *in a standard 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 as claimed in the instant application and described above.

Appx7095 (underlining in original; italics added).

3. Actavis filed an ANDA with a Paragraph IV certification seeking to market a generic version of Contrave before the Orange Book-listed patents expired. Op. 6. Nalpropion's predecessor-in-interest (*see* Op. 3 n.1) sued for infringement. By the time of trial, Actavis challenged two asserted claims of the '111 and '626 patents as obvious, and claim 11 of the '195 patent as lacking written description. Op. 6.

After a bench trial, the district court ruled for the patentees. Op. 6-7. As relevant here, the district court concluded that the specification's failure to disclose a formulation with the claimed dissolution profile obtained using USP 2 did not present a written-description problem because the USP 1 and USP 2 were

"substantially equivalent" dissolution methods. Op. 6. Thus, the court determined that whether Example 2 and Example 3 used USP 1 or USP 2 was not relevant. Op. 9.

4. The panel affirmed in part and reversed in part. The Court unanimously agreed with Actavis on obviousness,[2] but, over the dissent of Chief Judge Prost, a majority affirmed the district court's determination that the specification provided adequate written-description support for claim 11. The majority acknowledged that claim 11 "requires that the claimed naltrexone formulation have an in vitro dissolution profile in a dissolution test of USP Apparatus 2 Paddle Method." Op. 8. The majority also acknowledged that nothing in the specification disclosed that the inventors achieved that dissolution profile using USP 2, and that Example 2 of the specification disclosed the use of USP 1. Op. 8-9. But the majority held that the difference between the claim limitation and the disclosures in the specification was irrelevant, because the district court found that a skilled artisan would understand USP 1 and USP 2 to be "substantially equivalent" methods for testing dissolution profile. Op. 11.

Critical to the majority's conclusion was its observation that claim 11's requirement that the dissolution profile be measured by USP 2 "relates only to the measurement of resultant in vitro parameters, not to the operative steps to treat

[2] Nalpropion has not sought rehearing of that holding.

overweight or obesity." Op. 10. The majority stated that "[w]hile 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." Op. 12. Because the claim limitation was not an "operative claim step[]," the majority concluded that "[r]igidity should yield to flexible, sensible interpretation." *Id.*

4. Chief Judge Prost dissented from this portion of the opinion, stating that she would have found claim 11 invalid for lack of adequate written description. Chief Judge Prost observed, among other things, that the majority created "a new rule" by holding "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,'" and that this "'substantially equivalent' rule is inconsistent with this court's precedent." Dissent 2. Chief Judge Prost explained that this Court's en banc decision in *Ariad* and its decision in *Lockwood* make clear that "[a] substantially equivalent disclosure, even if it would render the claim limitation obvious, cannot satisfy the written description requirement," but the majority's "substantially equivalent" rule permits exactly that. Dissent 6.

## ARGUMENT

### I. The Majority's "Substantially Equivalent" Rule Conflicts with this Court's Written-Description Precedents.

Until the panel majority's decision in this case, the written-description requirement was clear. The specification must "show that the inventor actually invented *the invention claimed*." *Ariad*, 598 F.3d at 1351 (emphasis added). And every limitation is equally material to the invention claimed. *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 988 (Fed. Cir. 1995), *aff'd*, 517 U.S. 370 (1996). This means that the entire claimed invention, including "all the [claim] limitations[,] must appear in the specification." *Lockwood*, 107 F.3d at 1572. Just disclosing enough to "render[] the invention obvious does not satisfy the requirement." *Ariad*, 598 F.3d at 1352; *accord Lockwood*, 107 F.3d at 1572.

Now, however, there are two conflicting rules, depending on whether the claim limitation is deemed an "operative step" or something else.[3] For "operative" steps, the *Ariad-Lockwood* rule still applies, and the specification must disclose

[3] Chief Judge Prost in dissent interpreted the majority opinion to read the USP 2 method claim element as non-limiting. As discussed *infra*, pp. 16-18, given that the parties and the district court uniformly understood this element to be limiting, and counsel for Nalpropion agreed at oral argument that it was limiting, Actavis assumes that the panel majority did not silently engage in a *sua sponte* claim construction and find this claim element non-limiting. Instead, Actavis understands the panel majority to have considered this claim element limiting but not "operative" and concluded that the written-description requirement applied differently to non-operative claims, as the opinion itself suggests. Op. 12.

what is *actually claimed*. But for non-"operative" steps, the panel majority's new rule applies, and the specification need only disclose that the inventor possessed something "substantially equivalent" to the claimed invention. This Court should rehear this case en banc to ensure that there is *one* written-description test.

This Court has long read Section 112 to require the inventor to disclose in the specification an invention that contains "*all* the [claimed] limitations." *Lockwood*, 107 F.3d at 1572 (emphasis added). This Court has already considered whether it is sufficient for the specification to disclose something short of the claimed invention, such as an "obvious variant." And the Court has consistently held that the answer is no. *Id.*; *accord, e.g.*, *Ariad*, 598 F.3d at 1352.

In *Lockwood*, for example, the patentee contended that although the specification failed to describe the claimed invention, it "would have been apparent to one skilled in the art" from what *was* disclosed. *Id.* at 1572. This Court rejected that argument, stating that "[t]he question is not whether a claimed invention is an obvious variant of that which is disclosed in the specification." *Id.* Instead, the specification must "describe an invention, and do so in sufficient detail that one skilled in the art can clearly conclude that the inventor invented *the claimed invention*." *Id.* (emphasis added).

Similarly, in *Lucent Technologies, Inc. v. Gateway, Inc.*, 543 F.3d 710 (Fed. Cir. 2008), this Court held that the written-description requirement was not

satisfied because the claimed method of coding an audio signal required the use of modified discrete cosine transform (MDCT) coefficients, and the specification did not mention MDCTs. *Id.* at 719. The Court stated that "[e]ven if the implementation of MDCTs into the claimed technology *would have been obvious to one of skill in the art*, … a demonstration of obviousness is not sufficient to show possession." *Id.* (emphasis added).

This Court reached the same conclusion in *ICU Medical, Inc. v. Alaris Medical Systems, Inc.*, 558 F.3d 1368 (Fed. Cir. 2009), in which the claims recited intravenous valves with and without spikes but nothing in the specification indicated that the inventor possessed a valve without a spike. *Id.* at 1372. This Court held that the "spikeless claims" lacked adequate written description, rejecting the patentee's argument that it was "enough that it would have been obvious to a person of ordinary skill that a [valve] could be used without a spike." *Id.* at 1379.

This rule exists because an applicant obtains a patent based on *an invention*, not based on her ideas about an invention that *might* work but that she never possessed. *See Ariad*, 598 F.3d at 1345. As one cannot obtain patent protection beyond her invention, "[w]hat is claimed by the patent application must be the same as what is disclosed in the specification." *Id.* at 1347 (quoting *Festo Corp.*, 535 U.S. at 736). Absent this requirement, an inventor could "pretend[] that his

invention is more than what it really is, or different from its ostensible objects." *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1561 (Fed. Cir. 1991) (citation omitted). Thus, the written-description analysis "compares the claims with the invention disclosed in the specification, and if the claimed invention does not appear in the specification … the claim … fails regardless whether one of skill in the art could make or use the claimed invention," *Ariad*, 598 F.3d at 1348.

The panel majority's decision squarely conflicts with this precedent by holding that the disclosure of a "substantially equivalent" invention to what is claimed—an even broader scope than the "obvious variants" this Court has previously rejected—can satisfy the written-description requirement.[4] The majority effectively acknowledged that its decision was contrary to this Court's precedents, recognizing that "as a general matter written description may not be satisfied by so-called equivalent disclosure." Op. 12. But it said that the general rule did not apply because the relevant claim limitation "relates only to resultant dissolution parameters rather than operative claim steps."

[4] To be sure, this Court has recognized that the specification need not use identical *language* to the claim term. *Lockwood*, 107 F.3d at 1572 ("the exact terms need not be used *in haec verba*"). But the difference here was not one of language—the specification disclosed a different method of measuring dissolution rates from what was claimed, and the unrebutted evidence was that the different methods produced different results.

The majority cited nothing for the proposition that a different written-disclosure rule can apply where the undisclosed claim limitation is deemed less important than the "operative" steps of a method claim. Nor could it have done so. Every claim step is material, *Warner-Jenkinson*, *Inc. v. Hilton Davis Chemical Co.,* 520 U.S. 17, 29 (1997), which is why "all of the elements and limitations" must be described in the specification, *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 926 (Fed. Cir. 2004) (citation omitted), and "each claimed step must be performed" to prove infringement. *David Netzer Consulting Eng'r LLC v. Shell Oil Co.,* 824 F.3d 989, 998 (Fed. Cir. 2016). There are no major (or "operative") claim steps entitled to enhanced protection and minor claim steps entitled to lesser protection.

Indeed, the panel majority's rule is squarely foreclosed by *Ariad*, which stated that the patent "must adequately describe *the claimed methods* for reducing [certain gene activity], including adequate description *of the molecules that Ariad admits are necessary to perform the methods*." 598 F.3d at 1355 (emphases added). So too here—the specification must describe not only the "operative claim steps" of administering a sustained-release formulation, Op. 12, but also the formulations "necessary to perform" that operative claim step, *Ariad*, 598 F.3d at 1355. There is no basis to relegate some claim limitations to second-class status.

This Court should rehear this case en banc to restore uniformity to this patentability requirement.

## II. The Majority's New Rule Replaces a Clear and Uniform Rule with a "Flexible" and Unpredictable Guideline.

The panel majority premised its new rule on a desire to avoid "[r]igidity" and a preference for a "flexible, sensible interpretation." Op. 12. But the majority has replaced a bright-line rule with an essentially ad hoc distinction: limitations that are deemed important must be in the written description, but limitations that are deemed less important need not.

This amorphous rule makes written-description disputes more complex and less predictable. Courts already referee disputes over whether certain claim language is limiting or non-limiting (though here, the parties and the district court understood the USP 2 element to be limiting). But if a claim term is limiting, the law was clear that it required support in the specification—until this case. Now, if the claims reach something similar to but substantively different from what is disclosed in the specification, courts must make the further judgment whether the undisclosed claim limitation is important enough to require actual disclosure (the *Ariad-Lockwood* rule) or just "substantially equivalent" disclosure. And the panel majority provided no guidance about how to make that judgment—*i.e.*, what makes a claim limitation minor (or non-"operative") enough for the new rule to apply. The outcome of written-description challenges will become considerably

less predictable. That unpredictability is particularly harmful in the context of pharmaceutical patents, as it discourages generic drug companies from bringing cost-effective therapies to market.

Moreover, the panel's new rule will encourage inventors to claim patent protection far beyond the invention they *actually possessed*. By allowing an inventor to claim something that he did not invent, the majority's decision encourages applicants to write their claims in a way that "overreach[es] the scope of the inventor's contribution to the field of art," which undermines the very purpose of § 112, ¶ 1. *Reiffin v. Microsoft Corp.*, 214 F.3d 1342, 1345 (Fed. Cir. 2000).

This is particularly true with respect to continuation practice (prevalent in the pharmaceutical field[5]), which allows patentees to seek new patents based on the specification of an earlier application. During this "continuation process," "[t]he written description doctrine prohibits new matter from entering into claim amendments." *Agilent Techs., Inc. v. Affymetrix, Inc.*, 567 F.3d 1366, 1379 (Fed. Cir. 2009). Because continuation applications claim priority to the original filing date of the parent application, continuations avoid intervening would-be-invalidating prior art. Thus, if merely "substantially equivalent" disclosures can

[5] Mark A. Lemley & Kimberly A. Moore, *Ending Abuse of Patent Continuations*, 84 B.U. L. Rev. 63, 69 (2004).

support new claims not disclosed in the specification, patentees can expand their claims beyond their invention "and date [the new matter] back to their original filing date, thus defeating an accurate accounting of the priority of invention." *Chiron Corp. v. Genentech, Inc.*, 363 F.3d 1247, 1255 (Fed. Cir. 2004). The majority's new written-description standard, which is not grounded in the statute, will therefore encourage precisely what the written-description requirement is intended to prevent.

## III. If the Panel Concluded *Sua Sponte* that the USP 2 Clause Is Not Limiting, Then the Case Must Be Remanded for Further Proceedings Based on That New Claim Construction.

To the extent the panel's opinion rests on construing the USP 2 clause as non-limiting, it should be amended to include a remand. The patent issued because the USP 2 requirement was added, and both parties *and* the district court understood that requirement to be limiting. Had there ever been any suggestion that the clause was not limiting, Actavis would have successfully challenged claim 11 as anticipated or obvious. Thus, if the clause is non-limiting, the case should be remanded to permit Actavis to take advantage of the new construction.

To be clear: Actavis does not read the decision as construing the clause as non-limiting. The majority opinion referred to the claimed dissolution profile as something that "[t]his method claim … requires," Op. 8, and it never stated expressly or otherwise that this clause was non-limiting. The parties treated the

USP 2 clause as limiting below,[6] the district court treated it as limiting, Dissent 5 & n.1, and Nalpropion conceded on appeal that it is limiting.[7] And as Chief Judge Prost noted, the prosecution history makes clear that this clause was material to patentability. Dissent 3-4; *see supra* p. 5. Given this background, it seems unlikely the panel silently engaged in a *sua sponte* claim construction and found the clause non-limiting.

The dissent, however, interpreted the majority opinion as holding that the USP 2 clause is non-limiting. Dissent 2, 4-5. If that were what the Court held, then the case would need to be remanded for further proceedings consistent with that new construction. As the examiner observed, without the claim language specifying that the dissolution profile had to be measured using USP 2, the claims could not be distinguished from Weber. Appx7088. The only reason the parties did not litigate below the novelty of this claim is that all parties and the district court understood the USP 2 clause to be limiting. If the panel *sua sponte* rejected that understanding and newly construed the USP 2 clause as non-limiting, then claim 11 is anticipated (or obvious), and the panel should amend its decision to

[6] *See, e.g.*, Appx12578-12579 (Plaintiff's Statement of Contested Facts, including contested facts regarding whether Actavis's accused product satisfied claim 11's dissolution limitation).

[7] Oral Argument at 22:45-23:03 ("Q: I mean, we're driven by the claim, even if the specification has other tests in it. We've got this test [USP 2] here right? Infringement is going to be determined by this test? A: Yes, your Honor.").

allow Actavis to assert such a challenge and submit evidence in support on remand.

## CONCLUSION

The petition for rehearing en banc should be granted.

Respectfully submitted,

*/s/ William M. Jay*

William M. Jay
Jaime A. Santos
GOODWIN PROCTER LLP
901 New York Avenue, N.W.
Washington, DC 20001
Tel.: (202) 346-4000

Alexandra D. Valenti
GOODWIN PROCTER LLP
620 Eighth Avenue
New York, NY 10018
Tel.: (212) 813-8800

*Attorneys for Defendant-Appellant Actavis Laboratories FL, Inc.*

Scott J. Bornstein
Jonathan D. Ball, Ph.D.
Richard C. Pettus
Justin A. MacLean
MetLife Building
200 Park Avenue
GREENBERG TRAURIG LLP
New York, NY 10166
Tel.: (212) 801-9200

October 16, 2019

**RULE 32(g) CERTIFICATE OF COMPLIANCE**

Undersigned counsel certifies that this motion complies with the type-volume limitation of Fed. R. App. P. 35(b)(2)(A) because it contains 3,900 words, excluding the parts of the motion exempted by Fed. R. App. P. 32(f).

Undersigned counsel further certifies that this brief complies with the typeface requirements of Fed. R. App. P. 32(a)(5) and the type style requirements of Fed. R. App. P. 32(a)(6) because this brief has been prepared in a proportionally spaced 14-point Times New Roman typeface using Microsoft Word 2010.

*/s/ William M. Jay*
William M. Jay

## CERTIFICATE OF SERVICE

I, William M. Jay, hereby certify that on October 16, 2019, a copy of the foregoing document, filed through the CM/ECF system, will be sent electronically to the registered participants as identified on the Notice of Electronic Filing (NEF) and paper copies shall be served by first class mail postage prepaid on all counsel who are not served through the CM/ECF system.

*/s/ William M. Jay*
William M. Jay

# ADDENDUM

# United States Court of Appeals for the Federal Circuit

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**NALPROPION PHARMACEUTICALS, INC.,**
*Plaintiff-Appellee*

**v.**

**ACTAVIS LABORATORIES FL, INC.,**
*Defendant-Appellant*

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2018-1221

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

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Decided: August 15, 2019

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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.

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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

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**NALPROPION PHARMACEUTICALS, INC.,**
*Plaintiff-Appellee*

**v.**

**ACTAVIS LABORATORIES FL, INC.,**
*Defendant-Appellant*

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2018-1221

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

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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.