NOTE: This disposition is nonprecedential.

United States Court of Appeals for the Federal Circuit

ENDO PHARMACEUTICALS INC., GRUNENTHAL GMBH,
Plaintiffs-Cross-Appellants

v.

TEVA PHARMACEUTICALS USA, INC., ACTAVIS INC., ACTAVIS SOUTH ATLANTIC LLC, WATSON PHARMACEUTICALS, INC., AMNEAL PHARMACEUTICALS OF NEW YORK, LLC, ROXANE LABORATORIES, INC., AMNEAL PHARMACEUTICALS, LLC, THORX LABORATORIES, INC., BARR LABORATORIES, INC., RANBAXY, INC., RANBAXY PHARMACEUTICALS, INC., SUN PHARMACEUTICAL INDUSTRIES, LTD., IMPAX LABORATORIES, INC.,
Defendants-Appellants

2015-2021, 2015-2022, 2015-2023, 2015-2024, 2015-2025, 2015-2026, 2015-2028, 2015-2031, 2015-2033, 2015-2034, 2015-2035, 2015-2041, 2015-2042, 2015-2046, 2015-2047, 2015-2049, 2015-2059, 2015-2060, 2016-1025, 2016-1060, 2016-1117, 2016-1118

Appeals from the United States District Court for the Southern District of New York in Nos. 1:12-cv-08060-TPG-GWG, 1:12-cv-08115-TPG-GWG, 1:12-cv-08317-TPG-

GWG, 1:12-cv-08985-TPG-GWG, 1:13-cv-00435-TPG-GWG, 1:13-cv-00436-TPG-GWG, 1:13-cv-03288-TPG, 1:13-cv-04343-TPG, 1:13-cv-08597-TPG, Senior Judge Thomas P. Griesa.

Decided: May 16, 2018

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Before MOORE, BRYSON, and HUGHES, *Circuit Judges.*

HUGHES, *Circuit Judge.*

Endo Pharmaceuticals Inc. and Grünenthal GmbH sued generic drug manufacturers under the Hatch-Waxman Act in the U.S. District Court for the Southern District of New York, alleging infringement of, among other patents, U.S. Patent Nos. 8,309,122 B2 and 8,329,216 B2.[1] These patents relate to a controlled re-

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[1] We grant the motions to voluntarily dismiss appeal nos. 15-2022, 15-2023, 15-2025, 15-2028, 15-2033, 15-2034, 15-2035, 15-2041, 15-2042, 15-2047, 15-2049, 15-2059, 15-2060, and 16-1118.

Earlier, we granted Grünenthal's motion to stay appeal nos. 15-2021, 15-2022, 15-2024, 15-2025, 15-2026, 15-

lease formulation of the painkiller opioid oxymorphone. The generic drug manufacturers argued generally that the asserted patents' claims were invalid or not infringed. The district court rejected those arguments and found all asserted claims of the '122 and '216 patents not invalid, and all but two asserted claims infringed. Because there is no reversible error in the district court's findings, we affirm.

I

A

Endo holds the approved new drug application for OPANA®ER, a controlled release formulation of the painkiller opioid oxymorphone. Endo also owns the '122 and '216 patents, each reciting a controlled release formulation of oxymorphone suitable for twelve-hour dosing and claimed to cover OPANA®ER.[2]

2028, 15-2031, and 15-2033, pending action by the U.S. Food and Drug Administration related to Endo's controlled release crush resistant formulation of the painkiller opioid oxymorphone. Grünenthal now requests that we maintain the stay until 30 days after the pending FDA action has completed. We have granted Endo's request to voluntarily dismiss its appeals, so Grünenthal's request for a continued stay is applicable only as to appeal nos. 15-2021, 15-2024, 15-2026, and 15-2031. Because the generic drug manufacturers party to those appeals represent that they have withdrawn their abbreviated new drug applications, we exercise our discretion to lift the stay and dismiss appeal nos. 15-2021, 15-2024, 15-2026, and 15-2031, but do so without prejudice. We thus do not address Grünenthal's arguments or its patents in this opinion.

[2] The two patents essentially have a common specification. The '122 patent issued from the U.S. Patent

Generic manufacturers Amneal Pharmaceuticals of New York, LLC, Amneal Pharmaceuticals LLC, Impax Laboratories, Inc., ThoRx Laboratories, Inc., Ranbaxy, Inc., Ranbaxy Pharmaceuticals, Inc., Sun Pharmaceutical Industries, Ltd., and Roxane Laboratories, Inc. (collectively, Amneal) as well as Actavis Inc., Actavis South Atlantic LLC, Teva Pharmaceuticals USA, Inc., Barr Laboratories, Inc., Watson Pharmaceuticals, Inc. (collectively, Actavis) filed abbreviated new drug applications (ANDAs) with the U.S. Food and Drug Administration, seeking its approval to market generic versions of OPANA®ER.[3] Endo then sued them for infringement of the '122 and '216 patents, asserting four claims of the '122 patent and sixteen claims of the '216 patent during a consolidated bench trial.

B

The asserted claims of the two patents generally recite the following categories of limitations:

(1) A "dissolution" or "release rate" limitation, which describes the release of oxymorphone at a specified rate and is measured using the "USP Paddle Method at 50 rpm in 500 ml media." *See, e.g.*, '122 patent, col. 26 l. 59–col. 27 l. 7.

(2) A pharmacokinetic limitation, which describes how OPANA®ER tablets affect the human body once

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Application No. 11/680,432. Unsurprisingly, both the '432 application and the '216 patent trace priority to the same parent application. The '432 application was also the subject of an earlier appeal here. *See In re Huai-Hung Kao*, 639 F.3d 1057, 1061–63, 1065–70, 1074 (Fed. Cir. 2011).

[3] At the time the district court decided this case, the FDA had approved Actavis's ANDA for a generic version of OPANA®ER, and Actavis had been actively marketing that generic.

ingested—where the limitation can be further grouped into four broad subcategories:

(a) an analgesic effect limitation, which provides that the tablet will provide pain relief for a certain duration;

(b) a food effect limitation, which describes blood concentration level of oxymorphone (recited in the patents as $AUC_{(0\text{-}inf)}$, area under the drug concentration-time curve from time zero hours to infinity, or as C_{max}, maximum observed drug concentration) upon dosing of controlled release oxymorphone in fed versus fasting conditions (the effect refers to a patient's physiological response to the drug after having eaten—a pronounced food effect means a patient experiences much higher concentrations of the active ingredient if he has recently eaten);

(c) a detectable level limitation, which states that ingesting the tablets claimed in the patents will produce detectable levels of oxymorphone and its metabolite 6-OH oxymorphone; and

(d) a multiple peaks limitation, which describes when and how often patients' blood will exhibit peak concentrations of oxymorphone and 6-OH oxymorphone (multiple peaks help prevent patients from building tolerance to the opioid).

Claim 1 of the '216 patent includes an analgesic effect limitation, a detectable level limitation, and a multiple peaks limitation:

> 1. An oral controlled release oxymorphone formulation, comprising:
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> a. about 5 mg to about 80 mg of oxymorphone or a pharmaceutically acceptable salt of oxymorphone; and
>
> b. a hydrophilic material,

> wherein upon oral administration of the formulation to a subject in need of an analgesic effect:
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> (i) the formulation provides detectable blood plasma levels of 6-OH oxymorphone and oxymorphone;
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> (ii) the blood plasma levels of 6-OH oxymorphone and oxymorphone peak within about 1 hour to about 8 hours after administration;
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> (iii) the blood plasma levels of 6-OH oxymorphone and oxymorphone exhibit a ratio of area under the curve ($AUC_{(0\ to\ inf)}$) of blood plasma level versus time for 6-OH oxymorphone compared to oxymorphone in a range of about 0.5 to about 1.5;
>
> (iv) the duration of the analgesic effect is through at least about 12 hours after administration; and
>
> (v) the blood plasma levels of oxymorphone exhibit *two or three peaks within about 12 hours* after administration.

'216 patent, col. 26 ll. 35–55 (emphases added).

Claim 38, a method claim from which the asserted claim 40 of the '216 patent depends, exemplifies a dissolution limitation and a C_{max}-related food effect limitation:

> 38. A method for treating pain in a human subject in need of acute or chronic pain relief, comprising the steps of:
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> (a) Providing a solid oral dosage form comprising about 5 mg to about 80 mg oxymorphone or a pharmaceutically acceptable salt thereof in a controlled release delivery system with a release rate profile designed to provide adequate blood plasma levels over at least 12 hours to provide sustained pain relief over this same period, wherein oxymorphone is the sole active ingredient, and where-

> in upon placement of the composition in an in vitro dissolution test comprising USP Paddle Method at 50 rpm in 500 ml media having a pH of 1.2 to 6.8 at 37°C., *about 15% to about 50%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 1 hour in the test, about 45% to about 80%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 4 hours in the test, and at least about 80%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 10 hours in the test*; and
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> (b) administering a single dose of the dosage form to the subject, wherein the oxymorphone C_{max} is at least 50% higher when the dosage form is administered to the subject under fed versus fasted conditions.

Id. at col. 29 l. 49–col. 30 l. 5 (emphases added).

Claim 40 of the '216 patent depends from claim 38, and recites an AUC-related food effect limitation: "the difference in the oxymorphone area under the curve *$AUC_{(0\text{-}inf)}$ between fed and fasted conditions is less than 20%*." *Id.* at col. 30 ll. 10–12 (emphasis added).

Endo asserted claims 2–3 and 19–20 of the '122 patent against all defendants. J.A. 18. Three of the four claims—claims 2–3 and 19—recite a dissolution limitation. Claim 20 recites a food effect limitation.

Endo also asserted sixteen claims of the '216 patent, claims 1, 22, 40, 42, 50, 54, 57, 62, 64, 71, 73–74, 78–80, and 82, but not all claims were asserted against all defendants. J.A. 28. Fifteen of the sixteen asserted claims recite dissolution limitations; claim 1 is the only asserted claim without a dissolution limitation. Claims 40, 42, 50, 54, 78, 80, and 82 also recite food effect limitations.

C

The district court concluded that the generic drug manufacturers failed to show that the asserted claims of the two patents are invalid. J.A. 128–29. Specifically, the court found that the asserted claims of the two patents are not invalid for obviousness; that the asserted claims with the dissolution limitations are not invalid for lack of written description; and that the asserted claims reciting the multiple peaks limitations are not invalid for indefiniteness. The court also found that Endo carried its burden to show that defendants infringe or will infringe all but two of the asserted claims of the '122 and '216 patents. J.A. 72–73. The court then issued a permanent injunction against Actavis's manufacture, use, offer to sell, or sale of its generic version of OPANA®ER prior to the expiration of the '122 and '216 patents. J.A. 182.

Both Amneal and Actavis appeal the district court's conclusions on invalidity. Amneal also appeals the court's infringement determination, and Actavis additionally challenges the permanent injunction against it.[4] We have jurisdiction under 28 U.S.C. § 1295(a)(1).

II

Obviousness is a question of law that we review de novo, and we review any underlying factual questions for clear error. *Honeywell Int'l, Inc. v. United States*, 609 F.3d 1292, 1297 (Fed. Cir. 2010). "Whether a claim satisfies the written description requirement is a question

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[4] Endo cross-appeals the district court's determination that the relief Endo requested under 35 U.S.C. § 271(e)(4) is not warranted. But Endo conceded at oral argument that its cross-appeal is conditional on our vacating the district court's grant of a permanent injunction. We affirm the district court in toto; thus, we need not reach Endo's cross-appeal.

of fact that, on appeal from a bench trial, we review for clear error." *Alcon Research Ltd. v. Barr Labs., Inc.*, 745 F.3d 1180, 1190 (Fed. Cir. 2014). Indefiniteness is a question of law that we review de novo, although any factual findings by the district court based on extrinsic evidence are reviewed for clear error. *UltimatePointer, L.L.C. v. Nintendo Co.*, 816 F.3d 816, 826 (Fed. Cir. 2016). Infringement is a question of fact that we review for clear error. *Alcon Research*, 745 F.3d at 1186. "The decision to grant or deny permanent injunctive relief is an act of equitable discretion by the district court, reviewable on appeal for abuse of discretion." *eBay Inc. v. MercExchange, L.L.C.*, 547 U.S. 388, 391 (2006).

A

Appellants first argue that the district court erred in concluding that the asserted claims are not invalid as obvious. We disagree. Appellants fail to carry their burden to show, by clear and convincing evidence, that the asserted claims would have been obvious because, among other things, the prior art references in the record strongly discourage a controlled release formulation of opioids with low bioavailability, such as oxymorphone, and, more critically, do not suggest the dissolution and pharmacokinetic limitations recited in the asserted claims of the '122 and '216 patents.

A claim is invalid if, at the time of invention, a person having ordinary skill in the art would have found the patented invention obvious in light of the prior art. *See* 35 U.S.C. § 103;[5] *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S.

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[5] Congress amended 35 U.S.C. § 103 in 2011 as part of the America Invents Act (AIA). *See* Leahy-Smith America Invents Act, Pub. L. No. 112-29, § 35, 125 Stat. 84, 341 (2011). References to § 103 and other sections of Title 35 of the United States Code in this opinion refer to

398, 415–16 (2007). A determination of obviousness is based on underlying factual findings, including what a prior art reference teaches, whether a person of ordinary skill in the art would have been motivated to combine references, and any relevant objective indicia of nonobviousness. *Apple Inc. v. Samsung Elecs. Co.*, 839 F.3d 1034, 1047–48, 1051 (Fed. Cir. 2016) (en banc). Patents are presumed to be valid and overcoming that presumption requires clear and convincing evidence. 35 U.S.C. § 282; *Microsoft Corp. v. i4i Ltd. P'ship*, 564 U.S. 91, 95 (2011).

Appellants argue that the district court failed to acknowledge that explicit disclosures in the prior art teach the use of oxymorphone in a controlled release formulation. They mainly rely on the following prior art references in the record:

(1) Maloney, a published patent application that discloses controlled release opioid formulations. The reference specifically discloses a dissolution profile for a controlled release formulation containing oxycodone, an opioid with markedly better bioavailability than oxymorphone, and teaches that its dosage form provides a dissolution rate of 60–80% active agent released after 12 hours. It also lists oxymorphone as a preferred opioid for use in its invention, alongside heroin, opium, and fentanyl.

(2) Oshlack, a U.S. patent which teaches that "dissolution time and . . . bioavailability . . . are two of the most significant fundamental characteristics for consideration when evaluating sustained-release compositions." J.A. 92. In describing suitable active ingredients, the refer-

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the pre-AIA version of the statute, the version that applies here.

ence includes opioid analgesics, listing 72 molecules including oxymorphone, heroin, opium, and fentanyl.

(3) Penwest S-1, a registration statement on Form S-1 filed with the U.S. Securities and Exchange Commission in 1997 by Penwest Pharmaceuticals, which discloses that Penwest was co-developing controlled release oxymorphone with Endo using Penwest's TIMERx system.

(4) Baichwal, a U.S. patent which teaches the use of the TIMERx system (the controlled release system Endo used in OPANA®ER) with a wide variety of active ingredients, including the analgesics aspirin, codeine, morphine, dihydromorphone, and oxycodone.

(5) Cleary, a research article published in 2000 in the "Cancer Control" journal that discloses that oxymorphone was under development in "sustained-release" formulation.

Amneal contends that the court erred by finding that oxymorphone's low bioavailability teaches away from attempting a controlled release formulation. Overwhelming evidence at trial, however, supports that factual finding. Expert testimony showed that a skilled artisan would not have been motivated to select oxymorphone for use in a controlled release setting because of its "exceptionally low bioavailability." J.A. 98. As the district court noted, the Oshlack reference also taught that "bioavailability is a significant, even crucial, factor in evaluating a drug's suitability for placement in a controlled release vehicle." J.A. 92. The court also observed that "[t]he notion that low-bioavailability drugs were considered unsuitable for extended-release formulation is reinforced by the fact that, until Endo's development of OPANA®ER, there were remarkably few such examples." J.A. 94. For example, the existence of another low-bioavailability drug, oxybutynin—a non-opioid analgesic, unlike oxymorphone—which had previously been developed into a controlled release formulation, served to underscore "the

fact that low bioavailability drugs were remarkably rare in controlled-release settings." J.A. 95. Indeed, "its total absence from the expert reports of both sides, impressed on the court that low-bioavailability drugs were, at the time of the invention, perceived as unsuited for development into controlled release forms." *Id.* Tellingly, Appellants' own expert maintained the view that active ingredients with poor bioavailability would not be good candidates for controlled release dose forms. J.A. 2769.

Appellants contend that the low bioavailability of oxymorphone could be addressed by increasing the dosage. The district court did not err in rejecting that argument. The court found, based on published research, that such an approach "risk[ed] toxicity." J.A. 93. As such, one of ordinary skill in the art would have been strongly discouraged from using a low bioavailability opioid like oxymorphone as the main ingredient in a controlled release formulation versus viable candidates such as oxycodone with reasonably high bioavailability. *See Allergan, Inc. v. Sandoz Inc.*, 796 F.3d 1293, 1305 (Fed. Cir. 2015) (explaining that the prior art teaches away when "a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant" (quoting *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994))). Relatedly, a skilled artisan would not have had a reasonable expectation that beneficial results could be achieved using a controlled release formulation of oxymorphone. *Cf. In re Merck & Co., Inc.*, 800 F.2d 1091, 1097 (Fed. Cir. 1986) (concluding that obviousness does not require absolute predictability, only a reasonable expectation that the beneficial result will be achieved).

Oxymorphone's inclusion in Maloney's and Oshlack's lists of candidate molecules does not alter this conclusion. Those lists mention oxymorphone among a vast number of other molecules, including drugs such as heroin, opium,

and fentanyl, so the district court doubted that the lists would be taken seriously as indicating suitability for controlled release treatment. J.A. 96–98. The court noted, for example, that fentanyl was widely understood as suitable only for transdermal, not oral, delivery. J.A. 96–97. Given that context, the district court reasonably found that a skilled artisan would not have viewed oxymorphone as suitable for a controlled release setting. Moreover, neither Penwest S-1 nor Cleary discloses any technical details, such as dosing interval or twelve-hour efficacy, for achieving the claimed inventions. J.A. 3144–45. Accordingly, a person of ordinary skill, upon reading those references, would have been strongly discouraged from using oxymorphone in a controlled release setting. The district court did not clearly err in finding that the references taught away from the claimed invention.

Actavis argues next that claim 1 of the '216 patent, which does not recite a dissolution limitation, claims no more than the combination of a known drug (oxymorphone) with a known controlled release platform (TIMERx), and recites pharmacokinetic observations from the administration of the obvious combination. The district court properly rejected that argument by crediting expert testimony demonstrating that a comparison of two controlled release drugs using the same controlled release technology exhibits significantly different formulations. J.A. 101–02; J.A. 3117–19. Although Actavis offered its own expert testimony, the district court found Endo's expert testimony more persuasive. We will not disturb the court's weighing of the evidence.

We also reject the argument that the district court erred in finding that no prior reference of record teaches the dissolution limitations. The Endo patents express the measurement of dissolution profile for controlled release oxymorphone using the USP Paddle Method at 50 rpm. *See* '122 patent, col. 25 l. 57. But the prior art references produced at trial measured dissolution in a different

manner. Maloney, for instance, measured dissolution of controlled release oxycodone using the USP Basket Method at 100 rpm. *See* J.A. 103. Oshlack measured dissolution using the USP Paddle Method, but did so at twice the speed, at 100 rpm, and in nearly twice the aqueous buffer (900 ml compared to Endo's 500 ml of media). *See id*. As the district court found, a person of ordinary skill in the art would not have expected a correlation between results obtained using the Paddle and Basket methods at different speeds because a significant body of art shows no such relationship. J.A. 104–07. In light of that finding and because there was no way to equate the results obtained from the different testing methods, a person of ordinary skill in the art would not have been able to extrapolate the dissolution limitations claimed in the '122 and '216 patents from the prior art.

Appellants argue further that the district court erred by giving patentable weight to the pharmacokinetic limitations inherent to the formulations disclosed by the prior art.[6] The district court found that none of the prior

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[6] Amneal relatedly asserts that the court legally erred by ignoring our relevant precedent in *Kao* in which, according to Amneal, we examined the Maloney reference and held, among other things, that the pharmacokinetic limitations are "inherent" properties of oxymorphone that add "nothing of patentable consequence." *Kao* is inapposite for two reasons. First, as an appeal from the Board of Patent Appeals and Interferences (BPAI), *Kao* involved a less fulsome record and a different evidentiary burden for showing obviousness. Second, the portion Amneal references in support of its argument pertains to a different application, not the '432 application that issued as the '122 patent. Indeed, Amneal glosses over our discussion in *Kao* that addressed the BPAI's factual findings related to the '432 application. The BPAI had found claims of the

art references in the record discloses the analgesic effectiveness of oxymorphone over a twelve-hour period; the claimed food effect limitations; the multiple peaks in blood concentration levels exhibited by controlled release oxymorphone over a twelve-hour period; or the detectable level limitations of the Endo patents. J.A. 113–15. By arguing that the pharmacokinetic properties are inherent in the controlled release formulation, Appellants put the cart before the horse: Endo does not claim any controlled release oxymorphone dosage for administration that *results* in the observed pharmacokinetic properties upon administration; it instead claims only those specific controlled release oxymorphone dosages that are *configured* to result in the observed pharmacokinetic properties upon administration. In other words, Endo does not claim *any* controlled release configuration of oxymorphone dosage, rather only those which have been specifically calibrated to produce the pharmacokinetic properties recited in the claims—excluding those that do not exhibit such properties. *See also* J.A. 111–12. Because the prior art did not give any indication to a person of ordinary skill that *oxymorphone* could have been developed into a controlled release formulation providing effective analge-

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'432 application reciting *dissolution* limitations obvious in light of Maloney. *See Kao*, 639 F.3d at 1061–63. We vacated and remanded, holding that the BPAI's factual findings in pertinent parts were unsupported by substantial evidence. *Id.* at 1065–70, 1074. On remand, the BPAI found the claims reciting dissolution limitations not invalid as obvious, reasoning that "the Examiner ha[d] not provided evidence or sound technical reasoning sufficient to show that the prior art would have directed those skilled in the art to a composition having the claimed dissolution rate." *Ex Parte Huai-Hung Kao*, 2012 WL 3307358, at *4 (B.P.A.I. Aug. 9, 2012). The '432 application then issued as the '122 patent.

sia over a twelve-hour period, the pharmacokinetic limitations were neither "necessarily . . . present" nor "the natural result of the combination of elements explicitly disclosed by the prior art." *PAR Pharm., Inc. v. TWI Pharm., Inc.*, 773 F.3d 1186, 1195–96 (Fed. Cir. 2014). For instance, Maloney teaches the analgesic effectiveness of a different molecule, oxycodone, but gave no indication of oxycodone's dosing interval. J.A. 97. It also does not indicate the dosing interval of sustained release oxymorphone. *Id.* Indeed, the inventor of the invention disclosed in Maloney herself acknowledged that her patent "application provides no clinical evidence that the formulations described in the application could be used to deliver oxymorphone in a manner sufficient to provide 12 hours of analgesia." J.A. 8926. The same is true of the other prior art references, which show dissolution, and in some instances sustained analgesia, for molecules other than oxymorphone. J.A. 114 (citing Oshlack and Baichwal, among other references).

Nor do any of the prior art references disclose the claimed food effect limitations. The district court noted that defendants made no attempt at trial to show some teaching in the prior art of the food effect of controlled release oxymorphone. J.A. 109. Indeed, Appellants fail to identify any prior art that discloses developing oxymorphone into a controlled release formulation based on the claimed AUC and C_{max} values under fed and fasted conditions. As the district court aptly noted,

> oxymorphone, when administered in an immediate release formulation, produces a total blood concentration (AUC) of 30% under fed conditions. This is considerably higher than the food effect of controlled release oxymorphone, which when taken under fed conditions produces total blood concentration (AUC) of 20%. If the food effect of oxymorphone was merely a result of natural processes, then one would expect the same total blood

> concentration (AUC) after eating for both the immediate release and controlled release formulations.

J.A. 109–10 (citations omitted).

The district court also relied on secondary considerations, which "strongly indicate[d]" the non-obviousness of the invention. J.A. 129. Endo's expert on commercial success established that OPANA®ER achieved tremendous sales growth since its launch. J.A. 120–21. The expert also demonstrated a clear nexus between the asserted claims of the two patents and the market success of OPANA®ER. *See, e.g.*, J.A. 2438–39. It was undisputed that OPANA®ER embodied the asserted claims.

Endo's expert on long-felt need separately testified that the medical community had long sought to effectively combat chronic pain, but the numerous immediate release opioids on the market had a short duration of effectiveness and often involved inconvenient routes of administration. J.A. 121, 1354–55, 1369. Moreover, after Endo demonstrated significant growth in sales and prescriptions, other companies decided to develop their own controlled release oxymorphone products. J.A. 2419.

On balance, Appellants fail to carry their burden to show, by clear and convincing evidence, that claims reciting the dissolution and pharmacokinetic limitations are fairly suggested by any prior art of record or combination thereof. The district court therefore did not err by concluding that the asserted claims of the '122 and '216 patents are not invalid as obvious.

B

Appellants next argue that the district court erred by concluding that the asserted claims of the '122 and '216 patents that recite the dissolution limitations are not invalid for lack of written description in the specification. Because the specification provides adequate support for

the dissolution or release rate limitations recited in the relevant claims, we disagree.

The written description requirement provides that a patentee's application for a patent must "clearly allow persons of ordinary skill in the art to recognize that [he] invented what is claimed." *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc) (quoting *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991)). "[T]he 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.*

Actavis argues that the asserted claims reciting the dissolution limitations claim a much broader range of release rates (15–50% of the drug after one hour, 45–80% after four hours, and more than 80% after ten hours), but the specification discloses much narrower ranges of release rates (27.8–32.3% at one hour, 58.1–66.9% at four hours, and 85.3–95.8% at ten hours) for formulations having 12 hours of analgesic efficacy. The allegedly expansive claims Actavis refers to in its argument—claim 1 of the '122 patent, for instance—recite "[a]n analgesically effective controlled release pharmaceutical composition with a twelve hour dosing interval in the form of a tablet, comprising oxymorphone or a pharmaceutically acceptable salt thereof as the sole active ingredient in the tablet . . . ." '122 patent, col. 26 ll. 59–63. Actavis contends that nothing in the specification explains or supports the dramatic extrapolation from the narrow range tested by the inventors during the clinical trials.

Actavis, however, plucks the release rates out of the cabined context in which the rates are disclosed: those specific release rates reflect the results from the administration of a *20 mg oxymorphone hydrochloride dosage*. *Id.* at col. 10 ll. 21–64. As the district court noted, the

specification is replete with additional examples of dosages satisfying each of the claimed limitations. J.A. 126–27. The specification clearly explains that an analgesically effective dosage could contain as low as about 5 mg to as high as about 80 mg of oxymorphone hydrochloride. '122 patent, col. 4 ll. 37–39. Accordingly, Endo is entitled to claim not just the narrower range based on a 20 mg dosage, but a broader range based on 5 mg to 80 mg dosage—and that is exactly what it did in the claims reciting the dissolution limitations.

The specification also discloses several different techniques for producing the oxymorphone controlled release oral solid dosage form of Endo's invention. *See id.* at col. 5 l. 44–col. 9 l. 28. The district court found, for instance, that the specification gives detailed descriptions of the in vitro and in vivo testing methods employed by Endo in developing the controlled release tablets. J.A. 127. Based on such disclosures, a person of ordinary skill in the art would recognize that Endo possessed the invention claimed. Nothing in our controlling precedent requires patent owners to test release rates for each dosage level before claiming such rates in the patents. Accordingly, the inventors chose ranges encompassing the invention while allowing for variations, as the court correctly noted.

The district court therefore did not err by concluding that the asserted claims of the '122 and '216 patents that recite the dissolution limitations are not invalid for inadequate written description.

C

Appellants next argue that the district court erred in concluding that the asserted claims that recite the multiple peaks limitations are not invalid for indefiniteness. Because the specification sufficiently describes the meaning and scope of the multiple peaks limitations, we disagree.

Claims are indefinite when "read in light of the specification delineating the patent, and the prosecution history," they "fail to inform, with reasonable certainty, those skilled in the art about the scope of the invention." *Nautilus, Inc. v. Biosig Instruments, Inc.*, 134 S. Ct. 2120, 2124 (2014). "Even if a claim term's definition can be reduced to words, the claim is still indefinite if a person of ordinary skill in the art cannot translate the definition into meaningfully precise claim scope." *Halliburton Energy Servs., Inc. v. M-I LLC*, 514 F.3d 1244, 1251 (Fed. Cir. 2008).

Amneal argues that claims 1, 71, and 78 of the '216 patent are invalid for indefiniteness because the claims recite the term "peaks," contending that the patents contain no explanation of how peaks should be measured or what constitutes peaks. That argument lacks merit. The district court noted that the specification refers to peaks of curves drawn on charts. J.A. 29 (referencing '216 patent, col. 12 ll. 58–67). Upon looking at the charts in the specification, the court found a skilled artisan would recognize a peak as occurring where blood concentration of oxymorphone reaches a high-point before declining. J.A. 29–30 (referencing '216 patent, fig. 5). In fact, the court's definition of the term peaks is no different from that offered by Appellants' own expert at trial. *See* J.A. 1997. Amneal cannot turn their back on that simple meaning and claim now that "'peak' as used in the patent had some special meaning representing a level of some particular sufficient magnitude," Amneal's Br. 68, not apparent from the specification, which renders the term indefinite.

Indeed, peaks are readily ascertainable as plotted in Figure 5 of the '216 patent based on a plain inspection. First, that chart is plotted on the basis of specific set of data tabulated in the specification, *see* '216 patent, tbl. 5, so each peak on the chart is tied to a numerical value of the plasma concentration of oxymorphone specified in

Table 5. Second, each peak is easily identifiable contextually from the set of lower values adjacent to it as shown on the chart in Figure 5. Accordingly, Appellants merely fish for far more precision than "reasonable certainty" requires under our precedent. *See Nautilus*, 134 S. Ct. at 2124; *see also id.* at 2123 ("[S]ome modicum of uncertainty is the 'price of ensuring the appropriate incentives for innovation' . . . ." (citation omitted)).

In sum, the district court did not err by concluding that the asserted claims that recite the multiple peaks limitations are not invalid for indefiniteness.

D

Appellants also argue that the district court erred in finding that Endo showed infringement of all but two asserted claims of the '122 and '216 patents. Because the court properly credited the testimony of Endo's expert who relied on information on package inserts of the proposed generics, we disagree.

"[T]he infringement inquiry called for by § 271(e)(2) is 'whether, if a particular drug *were* put on the market, it *would* infringe the relevant patent' in the usual, non-artificial sense." *Acorda Therapeutics Inc. v. Mylan Pharm. Inc.*, 817 F.3d 755, 760 (Fed. Cir. 2016) (citations omitted), *cert. denied sub nom. Mylan Pharm. v. Acorda Therapeutics*, 137 S. Ct. 625 (2017). The inquiry therefore focuses on a comparison of the asserted patent claims against the ANDA product that is likely to be sold following FDA approval. *Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1365–66 (Fed. Cir. 2003) (citing *Glaxo, Inc. v. Novopharm, Ltd.,* 110 F.3d 1562, 1567–68 (Fed. Cir. 1997)). Infringement exists if the defendants' product, as described in their ANDAs, meets each and every element of the asserted claims. *Sunovion Pharm., Inc. v. Teva Pharm. USA, Inc.,* 731 F.3d 1271, 1278 (Fed. Cir. 2013).

Amneal argues that the district court erred in finding infringement because the ANDA products do not infringe the "food effect" limitations. But the court found that "[d]efendants' package inserts expressly state that their products satisfy the AUC and C_{max} limitations of the '122 and '216 patents." J.A. 64–65 (citing to the package inserts). There is no basis to disregard the information contained on the package inserts, which are representations made to the FDA to establish that the proposed generics possess the same characteristics, including the food effect limitations, present in Endo's approved products. Thus, the court did not clearly err by finding infringement of all but two of the asserted claims of the patents.

E

Actavis finally argues that the district court abused its discretion by entering a permanent injunction against the manufacture, use, offer to sell, or sale of its generic version of OPANA®ER prior to the expiration of the '122 and '216 patents. Because Endo presented evidence of irreparable harm as well as other factors supporting an injunction, we conclude that the district court did not abuse its discretion by enjoining Actavis.

35 U.S.C. § 283 provides that a district court may grant an injunction "to prevent the violation of any right secured by patent, on such terms as the court deems reasonable." A plaintiff seeking a permanent injunction "must demonstrate: (1) that it has suffered an irreparable injury; (2) that remedies available at law, such as monetary damages, are inadequate to compensate for that injury; (3) that, considering the balance of hardships between the plaintiff and defendant, a remedy in equity is warranted; and (4) that the public interest would not be disserved by a permanent injunction." *eBay*, 547 U.S. at 391.

Actavis mainly argues that the district court abused its discretion in enjoining Actavis's original formulation of controlled release oxymorphone because Endo presented no evidence at trial of irreparable harm. That is inaccurate. The district court found that Endo will likely suffer irreparable harm relying on, among other things, its subsidiary findings that: (1) Actavis's generic version of OPANA®ER infringed Endo's patents; (2) Endo and Actavis are direct competitors in the oxymorphone market; and (3) the introduction of additional generics into the market has led Endo to suffer past harms (losing its market share, cutting its sales force, reducing its promotional expenses, and changing its research and development strategies)—which would continue unabated in the absence of an injunction—and, relatedly, that Endo is also at risk of intangible harms such as "reputational, organizational, and administrative." J.A. 178–79. Among other evidence, the court credited trial testimony to that end. *See* J.A. 1272–73; *see also* J.A. 1306. Indeed, "[i]t was proper for the district court to consider evidence of past harm" to assess irreparable injury to Endo. *i4i Ltd. P'ship v. Microsoft Corp.*, 598 F.3d 831, 861 (Fed. Cir. 2010), *aff'd,* 564 U.S. 91 (2011); *see also Broadcom Corp. v. Emulex Corp.*, 732 F.3d 1325, 1338 (Fed. Cir. 2013) ("The district court determined that Broadcom and Emulex were competitors and that Broadcom lost market share while Emulex gained it—thus Broadcom established irreparable harm." (citation omitted)).

Endo relatedly demonstrated, mainly through trial testimony, that it had to lay off its sales force, which may damage its reputation in the market segment and make the company less attractive to potential new hires. The court found that such irreparable harm cannot be adequately addressed without an injunction. J.A. 179–80. Actavis, on the other hand, made no affirmative argument that it would suffer hardship from an injunction to counter Endo's likely hardship. J.A. 180–81. Finally, the

court also found that public interest favors Endo's right to exclude others as the rightful patent owner. J.A. 181–82. On balance, it cannot be said that the district court abused its discretion in weighing these factors in Endo's favor and granting permanent injunctive relief.

III

We have considered the remaining arguments and find them unpersuasive. Accordingly, we affirm the district court's final judgment on invalidity, infringement, and permanent injunction.

AFFIRMED