2014-1294

United States Court of Appeals for the Federal Circuit

PURDUE PHARMA L.P., THE P.F. LABORATORIES, INC., PURDUE PHARMACEUTICALS L.P., AND RHODES TECHNOLOGIES,

Plaintiffs-Appellants,

v.

EPIC PHARMA, LLC,

Defendant-Appellee.

Appeal from the United States District Court for the Southern District of New York in No. 1:13-cv-00683-SHS, Judge Sidney H. Stein.

(*Caption continued on inside cover.*)

BRIEF OF PLAINTIFFS-APPELLANTS PURDUE PHARMA L.P., THE P.F. LABORATORIES, INC., PURDUE PHARMACEUTICALS L.P., AND RHODES TECHNOLOGIES

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2014-1296

PURDUE PHARMA L.P., THE P.F. LABORATORIES, INC., PURDUE PHARMACEUTICALS L.P., AND RHODES TECHNOLOGIES,

Plaintiffs-Appellants,

v.

MYLAN PHARMACEUTICALS INC. AND MYLAN INC.,

Defendants-Appellees.

Appeal from the United States District Court for the Southern District of New York in No. 1:12-cv-02959-SHS, Judge Sidney H. Stein.

2014-1306, -1307

PURDUE PHARMA L.P., THE P.F. LABORATORIES, INC., PURDUE PHARMACEUTICALS L.P., AND RHODES TECHNOLOGIES, AND GRÜNENTHAL GMBH,

Plaintiffs-Appellants,

v.

AMNEAL PHARMACEUTICALS, LLC,

Defendant-Appellee.

Appeals from the United States District Court for the Southern District of New York in No. 1:11-cv-08153-SHS, Judge Sidney H. Stein.

(*Caption continued.*)

2014-1311, -1312, -1313, -1314

GRÜNENTHAL GMBH, PURDUE PHARMA L.P., THE P.F. LABORATORIES, INC., PURDUE PHARMACEUTICALS L.P., AND RHODES TECHNOLOGIES,

Plaintiffs-Appellants,

v.

TEVA PHARMACEUTICALS USA, INC.,

Defendant-Appellee.

Appeals from the United States District Court for the Southern District of New York in No. 1:11-cv-02037-SHS and 1:12-cv-05083-SHS, Judge Sidney H. Stein.

CERTIFICATE OF INTEREST

Pursuant to Federal Circuit Rule 47.4, counsel for Plaintiffs-Appellants certifies as follows:

1. The full name of every party represented by me in this case is:

   Purdue Pharma L.P., The P.F. Laboratories, Inc., Purdue Pharmaceuticals L.P., and Rhodes Technologies

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:

   None

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 or are expected to appear in this court are:

   Ropes & Gray LLP: Kelly L. Baxter (no longer with firm), Kerstyn H. Crumb, Barna De, Sona De, Robert J. Goldman, Adrienne P. Hale, Christopher J. Harnett, Pablo D. Hendler, Rebecca R. Hermes, Phillip R. Kurs, Vikram A. Mathrani, Crystal Lohmann Parker, Matthew E. Prosen, Rebecca L. Rabenstein, Vincent C. Sica, Thomas A. Wang.

   Jones Day: Gregory A. Castanias, John J. Normile, Lynda Q. Nguyen, Jennifer L. Swize.

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TABLE OF ABBREVIATIONS

The following abbreviations are used in this brief. Emphasis throughout the brief is added unless otherwise noted.

Abbreviation	Term
’072 patent	U.S. Patent No. 7,683,072
’314 patent	U.S. Patent No. 7,776,314
’383 patent	U.S. Patent No. 8,114,383
’799 patent	U.S. Patent No. 7,674,799
’800 patent	U.S. Patent No. 7,674,800
14-hydroxy	14-hydroxycodeinone
8,14-dihydroxy	8,14-dihydroxy-7,8-dihydrocodeinone
8α	8α, 14-dihydroxy-7,8-dihydrocodeinone
8β	8β, 14-dihydroxy-7,8-dihydrocodeinone
ABUK	α, β-unsaturated ketone
A__	Appendix page
Amneal	Amneal Pharmceuticals, LLC
ANDA	Abbreviated New Drug Application
API	active pharmaceutical ingredient
Chapman	U.S. Patent Application No. 11/391,897
Chiu	U.S. Patent No. 6,177,567
Defendants	Teva Pharmaceuticals USA, Inc., Epic Pharma, LLC, Mylan Pharmaceuticals Inc.; Mylan Inc.; and Amneal Pharmaceuticals, LLC
Epic	Epic Pharma, LLC
FDA	U.S. Food and Drug Administration
Grünenthal	Grünenthal GmbH
Grünenthal Br.	Brief of Plaintiff-Appellant Grünenthal GmbH
low-ABUK patents	’072, ’799, and ’800 patents
McGinity application	WO 97/49384
Mylan	Mylan Pharmaceuticals Inc. and Mylan Inc.

TABLE OF ABBREVIATIONS
(continued)

NDA	New Drug Application
Plaintiffs	Purdue Pharma L.P.; The P.F. Laboratories, Inc.; Purdue Pharmaceuticals L.P.; Rhodes Technologies; and Grünenthal GmbH
PEO	polyethylene oxide
ppm	parts per million
Proksa	Bohumil Proksa, *10-Hydroxythebaine*, Arch. Pharm. Pharm. Med. Chem. 332, 369-70 (1999)
PTO	U.S. Patent and Trademark Office
Purdue	Purdue Pharma L.P.; The P.F. Laboratories, Inc.; and Purdue Pharmaceuticals L.P. (alternatively, also Rhodes Technologies)
Ramanathan	Ramanathan et al., *Dihydrocodeine, Dihydrocodeinone, 14-Hydroxydihydrocodeinone & Their Derivatives*, Indian Jour. of Technology, Vol. 2, No. 10, 350-351 (1964)
Rhodes	Rhodes Technologies
Teva	Teva Pharmaceuticals USA, Inc.
Weiss	Weiss, *Derivatives of Morphine. II. Demethylation of 14-hydroxycodeinone. 14-Hydroxymorphinone and 8,14-Dihydroxydihydromorphinone*, 22 J. Org. Chem. 1505-08 (1957)

STATEMENT OF RELATED CASES

These appeals have been consolidated as reflected in the caption above.

This Court's decision in *Purdue Pharma L.P. v. Teva Pharmaceuticals USA, Inc.*, Nos. 2014-1311, -1312, -1313, and -1314, will directly affect this Court's decision in the related appeals: *Purdue Pharma L.P. v. Epic Pharma, LLC*, No. 2014-1294; *Purdue Pharma L.P. v. Mylan Pharmaceuticals Inc.*, No. 2014-1296; and *Purdue Pharma L.P. v. Amneal Pharmaceuticals, LLC*, Nos. 2014-1306 and -1307.

STATEMENT OF JURISDICTION

The district court had jurisdiction under 28 U.S.C. §§ 1331 & 1338(a). In final judgments in Plaintiffs' actions against Teva, the court disposed of all claims and counterclaims between those parties. A116-22; A240-44; A5961-96. On January 29, 2014, the court adopted its invalidity determinations from the Teva cases and disposed of all claims and counterclaims involving Epic, Mylan, and Amneal. A251-53; A257-59; A7804-08. Purdue timely filed notices of appeal in all actions. A623; A625-27; A644; A647-48; A671-72; A690; A697. This Court has jurisdiction under 28 U.S.C. § 1295(a)(1).

STATEMENT OF THE ISSUES

1. The inventions claimed in the '072, '799, and '800 patents are to oxycodone API or salt with low levels of a potentially genotoxic impurity (14-hydroxy) derived from a precursor compound designated as 8α. Did the district court err in finding those claims obvious, where—

(a) the court itself found that (i) the prior art did not disclose either oxycodone API with low levels of 14-hydroxy, or 8α; (ii) Purdue and Rhodes discovered 8α and its role in forming 14-hydroxy; and (iii) Purdue was the first to use this discovery to create the first oxycodone API with low levels of the 14-hydroxy impurity;

(b) the court wholly disregarded the "8α" limitations of the '072, '799, and '800 patents on the rationale that process or source limitations are "immaterial" to validity for product claims, contrary to this Court's case law and to a correct construction of the '072 and '799 claims; and

(c) objective, real-world evidence—including the failure of others, others' recognition of the patented inventions, and Purdue and Rhodes's commercial success due to the patented inventions—demonstrates nonobviousness?

2. The inventions claimed in the '383 patent are abuse-deterrent opioid formulations that are hard enough to resist crushing, yet still effectively deliver controlled release of the active ingredient. Did the district court err in finding

the ’383 claims anticipated and obvious, where—

(a) the supposedly anticipatory McGinity application does not disclose (i) “opiates and opioids,” (ii) “with abuse potential,” or (iii) “breaking strength of at least 500 N,” each of which is recited in the ’383 claims;

(b) the prior art did not teach the ’383’s inventive combination of an opioid tablet so hard it would deter abuse yet still effectively deliver API; and

(c) objective, real-world evidence—including FDA’s recognition of the value of the invention—demonstrates nonobviousness?

STATEMENT OF THE CASE

A. Preliminary Statement

The four patents on appeal each disclose and claim safer pharmaceutical compositions containing the pain reliever oxycodone. Oxycodone, in its hydrochloride salt form, is the API in Purdue’s commercially successful OxyContin® extended-release tablets. OxyContin® is a powerful pain reliever that, when taken properly, has alleviated the pain of millions of patients since its approval in late 1995, and has annual sales exceeding $2 billion. However, the original OxyContin® product posed two problems: (i) its oxycodone API contained a seemingly unremovable, potentially genotoxic impurity, 14-hydroxy (an alpha, beta unsaturated ketone, or ABUK), and (ii) abusers discovered they could easily crush the tablets (designed to deliver 12 hours of oxycodone when

taken intact) into a powder containing a large, immediately available quantity of oxycodone that could then be swallowed, snorted, or injected for an instant "high." Using the patented technologies, Purdue addressed those two problems. First, in 2005, Purdue incorporated into its original OxyContin® product the "low-ABUK" technology of the '072, '799, and '800 patents to achieve an API with low levels of 14-hydroxy. Second, in 2010, Purdue received FDA approval for, and launched, a new product—Reformulated OxyContin®—that, in addition to the low-ABUK technology, incorporated, *inter alia*, the crush-resistant, abuse-deterrent advancement of the '383 patent.

This product, which replaced the original tablets, had been broadly desired but never before known. Purdue and Rhodes had long been seeking a reduction of 14-hydroxy in oxycodone API, and FDA expressed its own concerns about 14-hydroxy in 2003. But achieving such a reduction baffled even the most skilled scientists. It was the inventors at Purdue and Rhodes who ultimately discovered that the underlying source of the 14-hydroxy was 8α, a previously unknown chemical entity. Based on 8α's unique properties, they then identified how to address that problem. Unbeknownst to those in the art, 8α was converting into 14-hydroxy when the oxycodone free base was being converted to the oxycodone salt API. Purdue and Rhodes's discovery of 8α, and its conversion to 14-hydroxy, was the critical discovery. Without it, no one would have known how to remove the

8α-derived 14-hydroxy to yield substantially pure oxycodone. By discovering the source of the problem, Purdue and Rhodes solved the problem and made a substantial contribution to the art—a patentable improvement by any measure, particularly under the Supreme Court's decision in *Eibel Process*.

As with the impurity problem, a solution to reduce the abuse of opioids in general, and OxyContin® in particular, had long eluded the marketplace. In searching for solutions, the art assumed that, to release the opioid, the opioid tablets could not be too hard. Thus, those in the art looking for means to deter abuse assumed that the tablets had to be crushable. Contrary to that understanding, the '383 patent was first to achieve a formulation hard enough to deter crushing yet still effective in delivering an extended-release dose of oxycodone when taken properly—and it did so in the face of skepticism, a long-felt but unmet need for abuse-deterrent opioids, and the repeated failures of others. Indeed, FDA recognized the patent's achievement in crush resistance as embodied in Reformulated OxyContin® by approving the first-ever, abuse-deterrent labeling for that new product, and by finding that, in comparison, the original, crushable, and withdrawn OxyContin® tablets (and generic copies of them) were no longer safe enough to be sold. The '383 patent, too, was a new, nonobvious, and important advancement.

B. The ’072, ’799, and ’800 Patents Claim New, Low-ABUK Products

The ’072, ’799, and ’800 patents are directed to a new oxycodone salt containing very low levels of the impurity 14-hydroxy. A27. 14-hydroxy is an “α, β [alpha, beta] unsaturated ketone”—“ABUK” for short. A825-26. ABUKs have chemical structures that make them potentially genotoxic, *i.e.*, they have the ability to react with and potentially damage a person’s DNA. *See Chapman v. Casner*, 315 F. App’x 294, 295 (Fed. Cir. 2009) (14-hydroxy is “potentially [geno]toxic”). The ’072, ’799, and ’800 patents are known as the “low-ABUK” patents because they define the claimed products as containing very low, previously unattainable levels of 14-hydroxy. The ’072 patent claims new oxycodone API compositions with low levels of 14-hydroxy (A27); the ’799 patent claims oral dosage forms, *e.g.*, tablets, comprising the new oxycodone compositions (*id.*); and the ’800 patent claims particular, enumerated processes for making the new oxycodone compositions and the products made by those processes (*id.*).

Purdue asserted claims 1, 4, and 5 of the ’072 patent, claims 3 and 19 of the ’799 patent, and claims 30-34 and 76-79 of the ’800 patent. All are product claims. Independent claim 1 of the ’072 patent recites: “An oxycodone hydrochloride active pharmaceutical ingredient having less than 25 ppm 14-hydroxy[], wherein at least a portion of the 14-hydroxy[] is derived from 8α.” A534 at 34:57-60. Dependent claims 4 and 5 recite less than 15 and 10 ppm 14-

hydroxy, respectively. A535 at 35:1-6. Claims 3 and 19 of the '799 patent recite similar products in "[a]n oral dosage form," "wherein at least a portion of the 14-hydroxy[] is derived from 8α[] during conversion of oxycodone free base to oxycodone hydrochloride." A476 at 35:8-15 & 36:32-34. Claims 30-34 and 76-79 of the '800 patent, all agree, are product-by-process claims rather than ordinary product claims, reciting "Oxycodone salt prepared according to the process of" claims 1 or 57 of the '800 patent. A505 at 35:49-59; A506 at 38:42-49.

1. Purdue and Rhodes's Discovery of 8α and Its Properties, and Their Solution to the 14-Hydroxy Problem

Before the low-ABUK inventions, oxycodone products contained high ABUK levels—as much as 5700 ppm 14-hydroxy. A1207; A42322-27. Given 14-hydroxy's potentially dangerous genotoxic effects, that high level was cause for concern. A43465. However, as recently as 2008, the "medical need" for oxycodone compelled FDA to maintain oxycodone products on the market, even though they had high ABUK levels. A1226; A43466. Still, for patient safety—as well as the possibility that FDA could change course and mandate it—Purdue, Rhodes, and others recognized a need to reduce ABUK impurities in their products.

a. The Prior Art

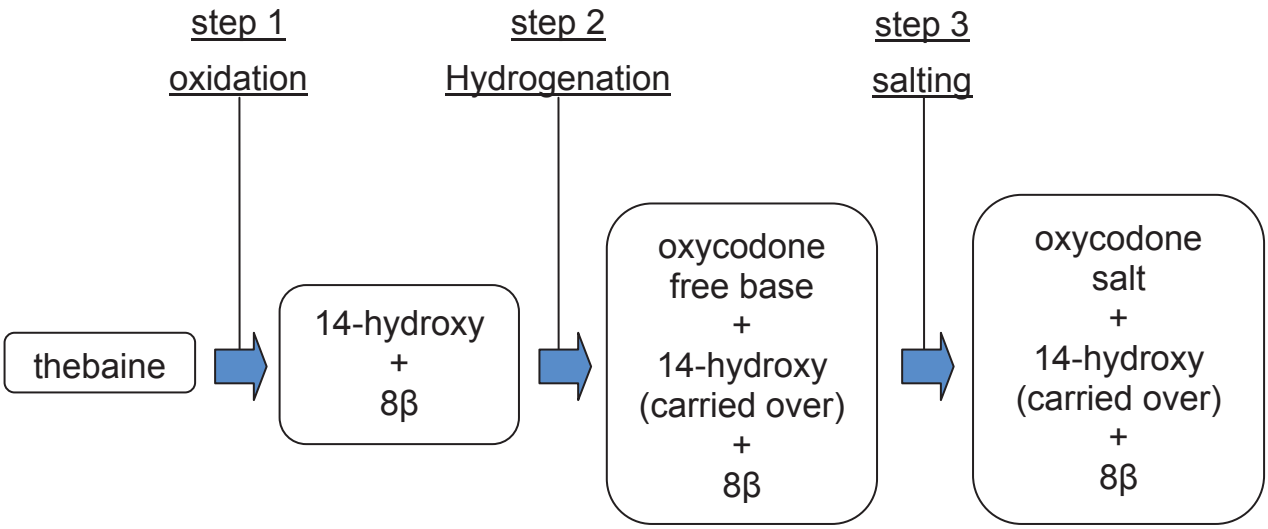
Rhodes collaborated with its associated company, Purdue, to make oxycodone API. Rhodes could not obtain FDA approval to sell *any* oxycodone API until it demonstrated to FDA that it could make that API with safe levels of

14-hydroxy. A22-23; A775; A780-84; A819; A1206-11; A42359-66. Since 2001, Rhodes had been seeking to reduce the levels of 14-hydroxy in the oxycodone API it was developing. A816-19; A825-27.

At the time, Rhodes's manufacturing process required three steps. A22. *First*, thebaine, a derivative of the opium poppy, was oxidized to form 14-hydroxy. A459 at 1:35-40, 1:64-65. *Second*, hydrogenation, activated by a catalyst, converted the 14-hydroxy to oxycodone free base. A459 at 1:66-67. *Third*, to convert oxycodone free base into salt, a stable and soluble form for general commercial distribution, the free base was reacted with hydrochloric acid to form oxycodone hydrochloride salt, the desired API. (This third step is commonly called "salting.") A477-535; A777-78; A822-25; A852; A1256; A1955; A45005-45131. The salt product, however, was not pure; 14-hydroxy was still present at relatively high levels (*e.g.*, 1500 ppm). A826.

Those in the art, including the Purdue and Rhodes scientists, thought that the 14-hydroxy created in step 1 had been carried through hydrogenation (step 2) and salting (step 3) to remain in the salt product. A23-24; A826-34; A1207; A41017; A42322-27. It was also understood that the oxidation of thebaine (step 1) created a benign compound known as 8β, 14-dihydroxy-7,8-dihydocodeinone ("8β"), a specific form of the chemical compound 8, 14-dihydroxy-7,8-dihydocodeinone identified by the orientation of one hydroxyl group (–OH), relative to another

hydroxyl group in the compound, at the 8 position.[1] A837-46; A906-17; A43497-43508; A44827-28; A44973-77; A44978-45002; A45139-42; A45244. Thus, the prior art assumed that the following reaction scheme took place:



Working with Purdue, Rhodes attempted to reduce the levels of 14-hydroxy

[1] As seen in the terms "8β" and "ABUK" (α, β-unsaturated ketone), scientific naming conventions are important to this appeal. As used in 8β, "β" ("beta") describes the three-dimensional orientation of one group relative to other groups in the compound. In general terms, when the compound is properly drawn on a piece of paper (the "plane") according to scientific conventions governing which way the compound is oriented, "beta" describes that the hydroxyl group (often designated as "–OH") points toward the viewer (*i.e.*, above the plane), whereas another term—"α" ("alpha")—describes that the hydroxyl group points away from the viewer (*i.e.*, below the plane). Thus, "8β" means that the hydroxyl at issue is at the "8 position" and points toward the viewer. As used in the term "ABUK," "alpha" and "beta" mean something entirely different—they describe the position of atoms that are double-bonded to one another relative to another functional group (*e.g.*, a ketone). For neither convention, however, do the terms "alpha" and "beta" indicate primacy. Thus, "alpha" and "beta" do not indicate that one form was discovered before or after the other. Additionally, the existence of a "beta" form (*e.g.*, 8β) does not presume the existence of a corresponding 8α form. A24-25; A1012-13; A1252-53; A2006.

in its oxycodone API. Rhodes first followed conventional wisdom and lengthened the time of hydrogenation when forming the free base—*i.e.*, Rhodes ran the hydrogenation to "completion"—to consume as much of the 14-hydroxy as possible. A821-22; A827-33; A1984-88; A41017; A45502-06; A47141; A45017-20. Initially, this seemed successful; the extended hydrogenation of step 2 appeared to have essentially eliminated the 14-hydroxy. As Rhodes's Dr. Kupper excitedly reported to Purdue's Board of Directors in September 2002, "[t]he numbers speak for themselves!" A830-33; A45502-06.

The enthusiasm was short-lived. Inexplicably, after the routine step of adding hydrochloric acid to convert the oxycodone free base to salt in the salting step (step 3), the levels of 14-hydroxy mysteriously reappeared in the salt, spiking upward to unacceptably high levels. A833-34. This surprised the scientists. A833-36; A1501-02; A9527-28. There was more to the story, but as yet no one knew what it was.

b. The Discovery of 8α

Purdue and Rhodes returned to the drawing board. The prior art was unhelpful. Having determined that, contrary to the teaching of the prior art, the 14-hydroxy in the salt had not simply been carried over from the hydrogenation step, but was instead *entirely new 14-hydroxy*, Purdue and Rhodes searched for the source of the mysteriously reappearing 14-hydroxy. A24-27. They "entered into a

research program to" (A) "understand where it [the new 14-hydroxy] was coming from," and (B) "remove it from our product." A835.

The possibilities were vast. The scientists analyzed the manufacturing process and the chemical reactions, products, and byproducts at the various stages of the process. For instance, they considered whether molecules known to form during oxidation of thebaine (step 1) were dehydrated by the acid of the salting step (step 3) to create the new 14-hydroxy. A838-39. Aware that 8β formed during oxidation, and notwithstanding the understanding in the art that the acid conditions in the salting step did not convert 8β to 14-hydroxy, Purdue and Rhodes researched that possibility. Their tests showed, however, that while the level of 14-hydroxy rose, the level of 8β remained the same, confirming that 8β was relatively stable in the acid conditions and did not convert to 14-hydroxy. A845-46; A906-07; A914-15; A44827-33; A44973-45002.

In 2002, Purdue and Rhodes developed another hypothesis: Perhaps a new, unknown molecule was being created during oxidation. A24; A840; A43497-43508. The prior art discouraged this theory—"since [this new molecule] wasn't reported in the literature, it probably didn't exist" (A843)—but Purdue and Rhodes pursued it anyway. Persistence paid off. They discovered that, contrary to all prior knowledge, the oxidation of thebaine was producing an entirely new molecule, having a molecular weight and structure similar to 8β, but with a different

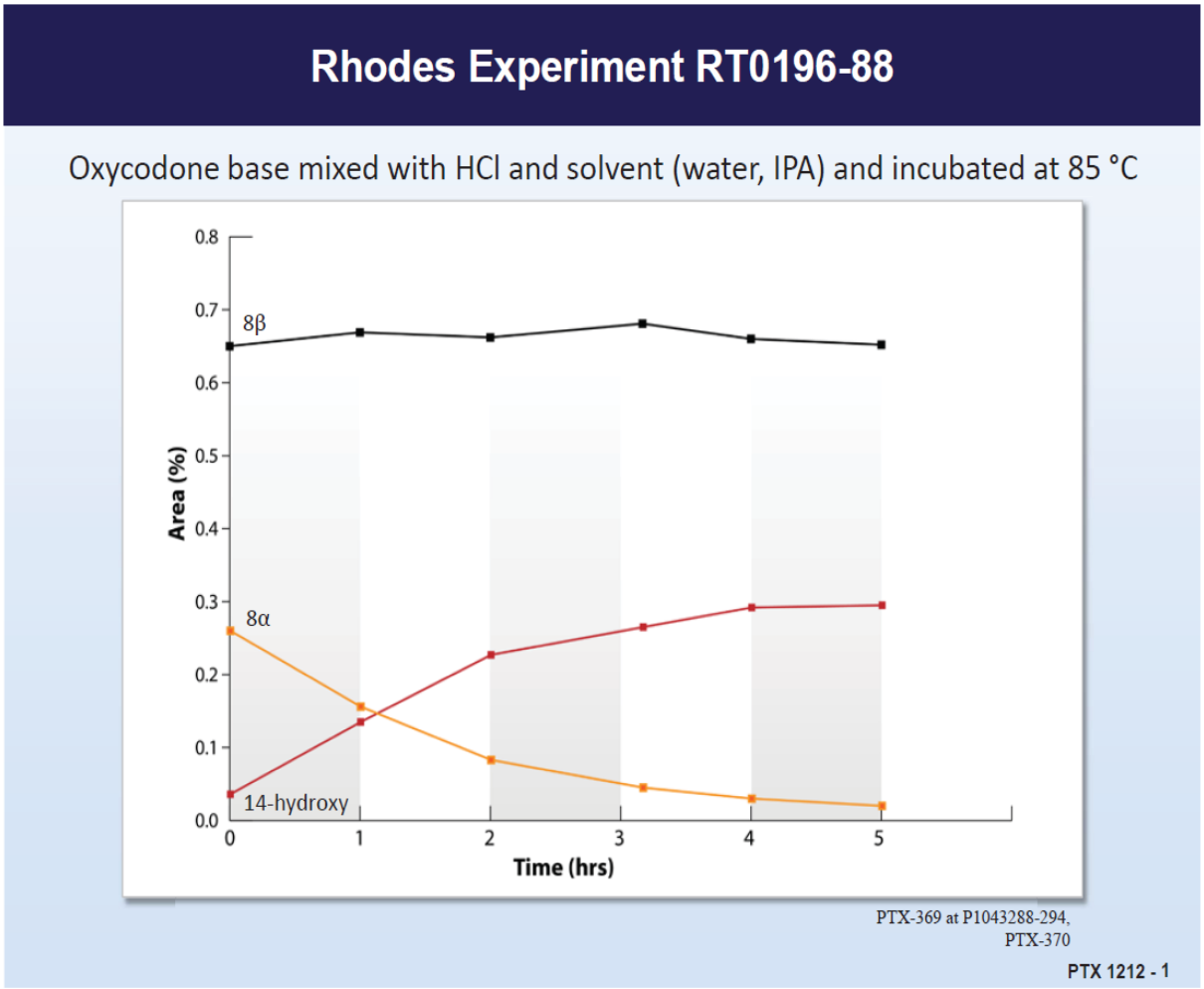
molecular orientation and different properties. A840-49; A863; A899-900; A908-16.

This new molecule was 8α. As the district court found, 8α had never been suggested, let alone known, in the art—Purdue and Rhodes were the first to discover it. A44; A50-51; A1989-91; A1995-96.

It turned out that 8α and 8β are "stereoisomers," and more particularly "diastereomers," of one another. A24-25; A1252-55; A1896. Isomers are different compounds with the same molecular formula—*i.e.*, the same component atoms—but arranged differently in space. A841. If the atoms have the same connections (bonds) to one another, but with different three-dimensional configurations, they are "stereoisomers." A1255. Where stereoisomers are not mirror images of one another, they are, as with 8α and 8β, "diastereomers." A876-77; A11957. As both sides' experts agreed, this seemingly slight structural difference causes the two diastereomers to have different physical and chemical properties, such as different melting points and reactivity with acid. A1848-49; A1858; A1995-98; A4261; A11957.

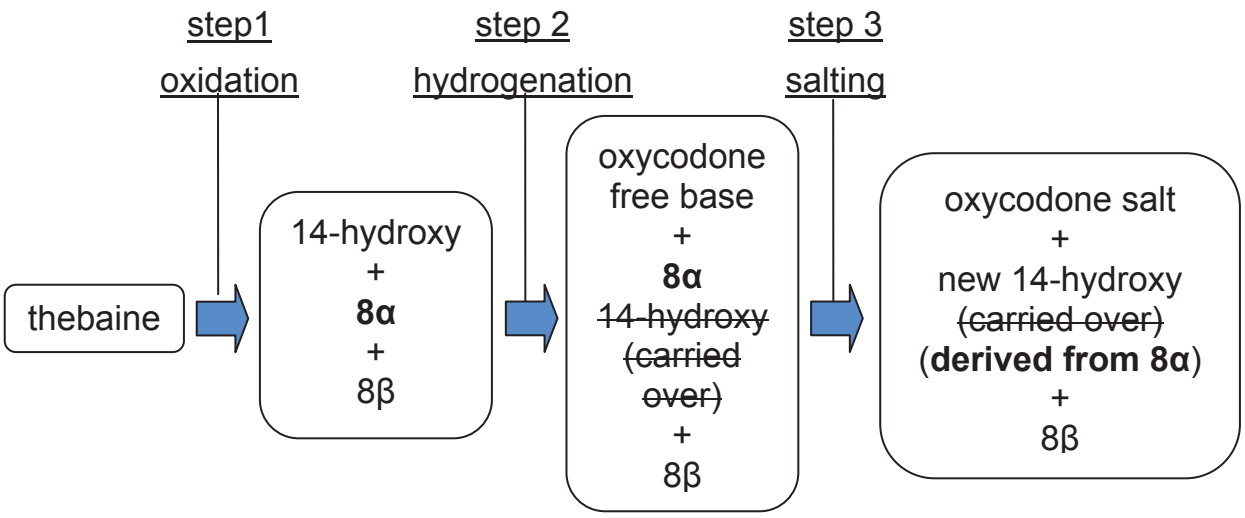
Purdue and Rhodes had discovered 8α, the source of the new 14-hydroxy that appeared in the salting step (step 3). A26. Through further testing and experimentation between November 2002 and February 2003, Purdue and Rhodes determined that the 8α present after oxidation of thebaine would decrease during

the salting step, and that the decrease in 8α occurred at an essentially 1:1 ratio to the appearance of the new 14-hydroxy in the salt product—proving their hypothesis that 8α was converting to 14-hydroxy. A840-49; A863; A899-900; A908-16. Unlike 8β, the levels of which remained constant with the addition of acid, the levels of 8α fell as levels of 14-hydroxy rose once acid was added. A26; A845-46; A906-17; A1281-83; A1997-2005; A44827-33; A44973-77; A44978-45002. The following graph shows, in orange and red lines, Purdue and Rhodes' discovery of the inverse relationship between 8α levels and 14-hydroxy levels, over time. A45458-59.



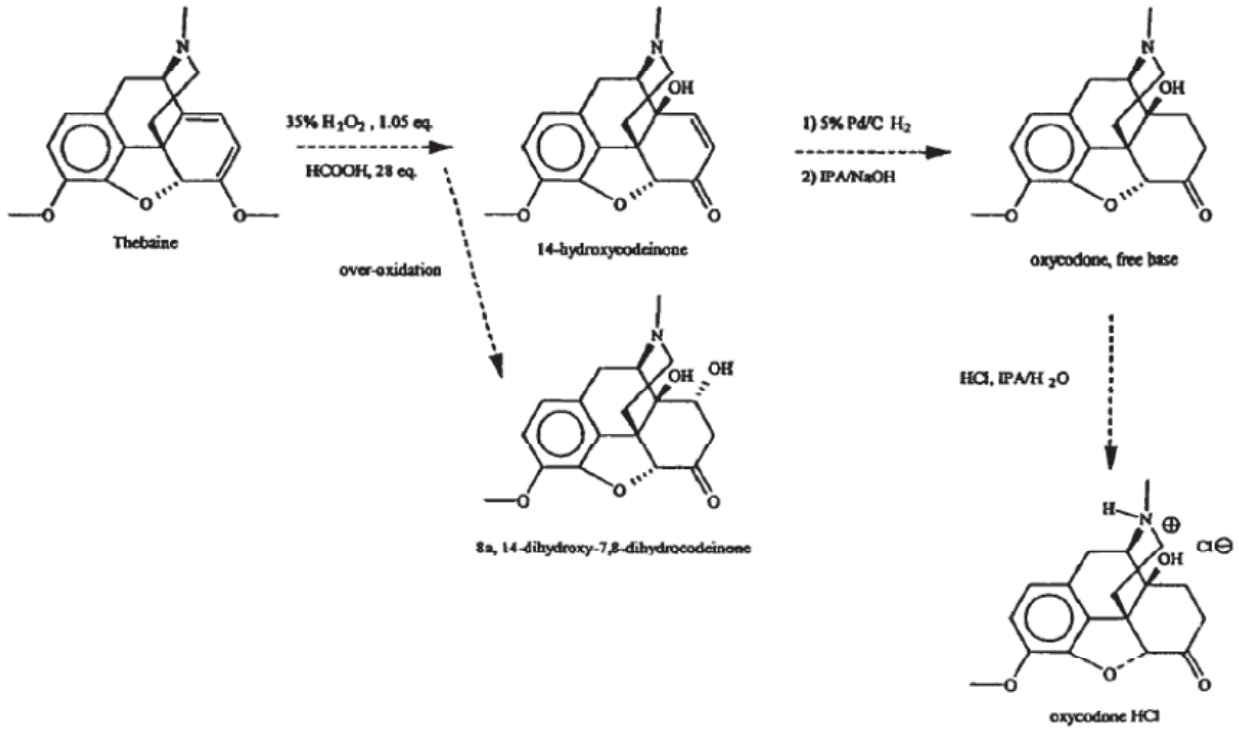
Purdue and Rhodes's work further led them to understand the properties of 8α. A person of ordinary skill would expect the properties of diastereomers to differ, but how and how much different they are cannot be known *a priori*. Their chemical properties must instead be studied. A1948; A2014. Purdue and Rhodes discovered that, unlike 8β, 8α is highly reactive with acid, so that adding acid in the salting step was converting 8α into the new 14-hydroxy. A835-38; A853. They thus concluded that the newly discovered 8α was created—along with the old 14-hydroxy—during oxidation of thebaine (step 1), that 8α "doesn't react in the

hydrogenation process" (step 2), and that 8α converts to the new 14-hydroxy during conversion of oxycodone free base to salt (step 3). A853-55. Contrary to the prevailing understanding in the art, Purdue and Rhodes discovered that the following reaction scheme was actually taking place, with their discoveries depicted in bold and strikethroughs:



This reaction is depicted in Figure 1 (below) of the low-ABUK patents (A853):

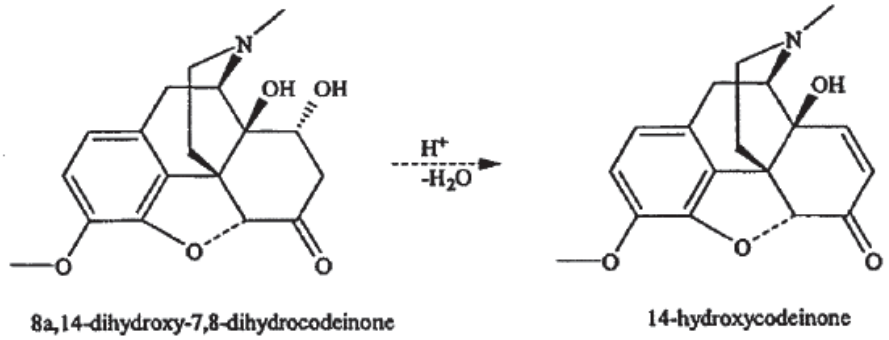
FIGURE 1



Reaction scheme of the process used to produce oxycodone HCl from thebaine.

A454. And Figure 2 (below) shows the conversion of 8α to 14-hydroxy when acid is added. "H^+" indicates the addition of acid, and "$-H_2O$" shows the dehydration of 8α (*i.e.*, the loss of a molecule of water).

FIGURE 2



8a,14-dihydroxy-7,8-dihydrocodeinone

14-hydroxycodeinone

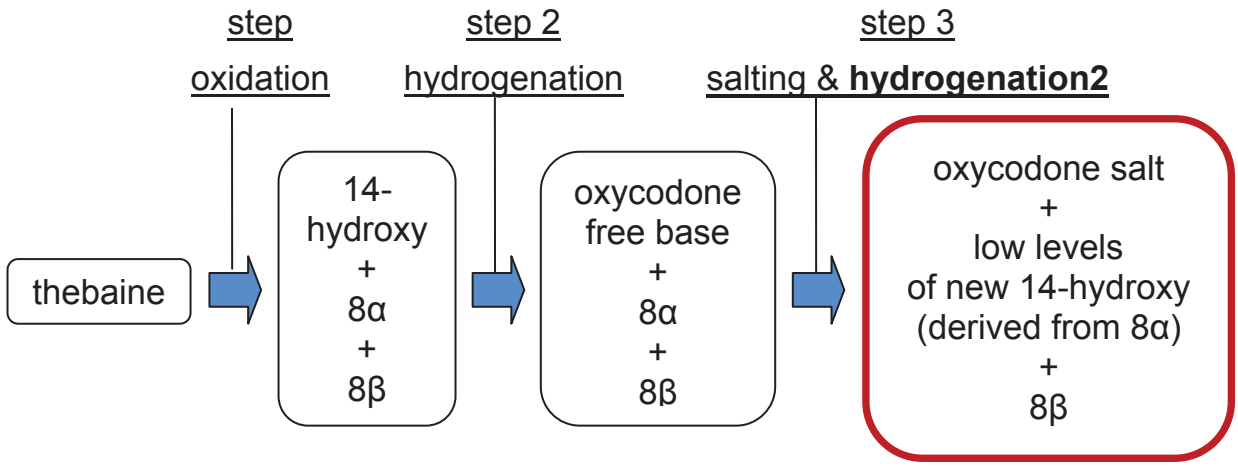
Dehydration of 8α, 14-dihydroxy-7,8-dihydrocodeinone

A455.

At that point, with their discovery of the existence of 8α, its properties, and its conversion to new 14-hydroxy when reacted with acid, Purdue and Rhodes finally had the key that unlocked the door of the never-before-solved mystery. Their discovery of 8α was a critical event in their efforts to address the appearance of new 14-hydroxy. They now could solve the problem by substantially reducing 8α, in turn minimizing the reappearance of 14-hydroxy in the salt. A848-49; A917 ("we began to examine methods for—methods for controlling the levels of 14-hydroxy[] in oxycodone hydrochloride based on this knowledge").

c. Designing a Novel Solution

Purdue and Rhodes finally solved the problem by designing a solution not previously taught or suggested in the art—a second hydrogenation step. This second hydrogenation step is different from the first hydrogenation step in two important ways. *One,* it uses different ingredients and reaction conditions specifically tailored to the particular properties of 8α. A859-62; A917-23. And *two*, it takes place *after* the formation of the oxycodone free base in step 2 (either after, or simultaneously with, step 3's reaction of free base with acid to form the salt). A849 ("The first [hydrogenation] step is run in water with formic acid. And the step that we're talking about here is run—the hydrochloride salt is already formed so you do not have to go through that formation step again."); A917-23; A996-99. Rather than the first hydrogenation, which takes place at step 2 and converts thebaine-derived 14-hydroxy to oxycodone free base, the second hydrogenation takes place at step 3 and is performed on the oxycodone salt (which remains oxycodone salt) and the 8α-derived 14-hydroxy. A27; A917-23; A997-98. Much of this new 14-hydroxy now forms oxycodone free base, which is converted to the salt. A849-50; A923-24. The following chart demonstrates the solution and the oxycodone product (indicated in red):



The patent specification and its examples show the 8α-specific solution. For instance, Purdue and Rhodes ran the second hydrogenation longer than usual because, even though the new 14-hydroxy appeared to be eliminated, the continuing reaction of 8α with acid would still convert 8α to 14-hydroxy. A461 at 6:53-54 ("[t]he composition is then hydrogenated under adequate conditions for a sufficient period"); A462 at 7:36-45 ("The total reaction time of the hydrogenation reaction is for a duration sufficient to reduce the content of the 14-hydroxy-codeinone to a level that is less than 25 ppm" and "can be, e.g., from about 10 minutes to about 36 hours"); A471; A922-35. And while one might repeatedly hydrogenate to try to reduce the level of 14-hydroxy, without knowing *why* longer hydrogenation would be necessary and what effects to counteract—*i.e.*, without knowing that the process for making oxycodone salt was creating *new* 14-hydroxy and that the new 14-hydroxy was from conversion of 8α—the ordinary artisan would not have applied hydrogenation (or any other technique) to the oxycodone

salt, as opposed to the oxycodone free base, or under conditions that would stop the continuing conversion of 8α to 14-hydroxy. A473-74; A1997-2005; A2010-14. Purdue and Rhodes also used specific acid amounts and specifically timed the removal of the catalyst, in response to the particular properties of 8α. A471; A4316-17. Without a solution specifically tailored to 8α and its unique properties, 8α would continue to convert to 14-hydroxy. A473-74; A2011-14.

Purdue and Rhodes had created a new product: oxycodone salt having very low levels of 14-hydroxy. Nothing in the prior art disclosed or suggested oxycodone salt having such low 14-hydroxy levels. And, nothing in the prior art taught or suggested the discovery that achieved that end. Until Purdue and Rhodes's discovery, it was unknown that the 14-hydroxy in the oxycodone salt was being newly created in the salting step (step 3), that 8α even existed (or what its properties were), or that it was the source of that 14-hydroxy. A1880-91; A1979-96; A4257; A4260. As one of the inventors explained: "In order to practice this invention, one has to understand where 14-hydroxy[] is coming from. Without that understanding, when trying to do this—these steps, one will not be able to achieve levels below what we specify as 25 parts per million." A951. By mid-2003, Rhodes was producing laboratory batches of oxycodone API containing the low 14-hydroxy levels recited in the patent claims, *e.g.*, 25 ppm or less. A848-51; A917-22; A45255-58; A45507-10.

2. FDA Approval of Purdue and Rhodes's Low-ABUK Oxycodone and the Efforts of Others

a. FDA Review

In February 2003, Purdue sought FDA approval for Rhodes as a new commercial manufacturer of oxycodone API. A1206-09; A4835-37; A42270-80. Levels of 14-hydroxy in Rhodes's product were already as low as 800-1600 ppm—substantially lower than the 3000-5700 ppm levels of Purdue's other suppliers (Noramco and Mallinckrodt). A827-28, A833; A1207-10, A1221; A41017; A42322-27. However, in January 2004, FDA declined to approve Rhodes's API product, instead insisting on no more than 10 ppm unless Rhodes could show that a higher level was not genotoxic. A775-84; A1206-11; A42359-66. FDA provided no suggestion as to how Rhodes might achieve such a low level. A780-84; A2014-16.

Purdue and Rhodes, striving to reach FDA's 10 ppm target, continued their work, including scaling up Rhodes's process for commercial production, and by February 2004 they were able to achieve 14-hydroxy levels as low as 500 ppm. A783-88. Purdue informed FDA of this result, and proposed a staged approval: Rhodes would make oxycodone for Purdue on an interim basis with no more than 500 ppm of 14-hydroxy, and would reach the 10 ppm goal by the end of 2004. A1212; A42359-63; A42375; A44059-60; A44067. Competitors' oxycodone API still contained 14-hydroxy as high as 2000 ppm (Noramco) and 2400

(Mallinckrodt). A1214-15; A42520; A42529. In March 2004, FDA agreed to this proposal. A1212-15; A42367-68.

By November 2004, ahead of schedule, Rhodes achieved 10 ppm of 14-hydroxy on a commercial scale, and Purdue sought unqualified approval for Rhodes, which FDA granted in March 2005. A783-92; A1216-18; A42786; A44059-99; A44124; A44400-06; A44971-72; A45511-12. That approval was critical to Rhodes's financial success, as it had recently invested $100 million to develop and expand its manufacturing capacity to make oxycodone for Purdue. A774; A781-83.

b. Failure of Others

Where Purdue and Rhodes succeeded in finding a low-ABUK formulation for oxycodone API, others failed. Although FDA began in 2003 to request other oxycodone manufacturers, new and old, to reduce their ABUK levels (A41007-09; A41014-15), none was able to do so until at least 2007, after Purdue and Rhodes's discovery and solution were published. Indeed, because no solution was yet known or suggested in the prior art, FDA understood that the industry needed time for research and experimentation, and initially let those manufacturers propose their own timelines. A805-06; A2014-15; A42359-66; A43464-74.

Noramco, which supplied oxycodone to both Purdue and Teva, failed. In 2004, when Rhodes was successfully reducing its levels from 500 to 10 ppm,

Noramco stated that FDA's 2003 request for a low-ABUK level "represents a technical and scientific challenge, both in the synthesis of oxycodone [salt] and analysis of the [14-hydroxy] impurity." A49; A2015-17; A41017. Only after Purdue and Rhodes's discovery of 8α became public (through publication of a priority application) did Noramco make any progress. Even then, Noramco took over three years—until 2007—to apply for its own patent related to low-ABUK formulations. And that application was based on, and specifically credited, Purdue and Rhodes's discovery of 8α and its role as the source of new 14-hydroxy in the salt. A51; A40851 at 3:60-63, 4:48-49, 4:54-61; *see also* A1295-96; A1302; A1527; A1532-34; A1627-29; A3978-79; A3982-84; A4072-73; A4229-33; A4236; A40445-46. Notwithstanding its patent, Noramco's oxycodone still infringed the low-ABUK patents, as the district court found. A33-39; A52-55.

3. The Low-ABUK Patents and Their Prosecution History

In 2004, Purdue and Rhodes filed provisional patent applications for their inventions, and the '072, '799, and '800 patents issued in March 2010, each with essentially the same written description. A448-76; A477-506; A507-35; A1256. The asserted claims specify "purity" levels of the oxycodone salt, expressed either as a requirement that the oxycodone salt be "substantially free" of 14-hydroxy (certain asserted claims of the '800 patent) or as a ppm cap on 14-hydroxy (the remaining asserted claims). A475-76 at 34:54-36:14; A504-06 at 34:22-38:53;

A534-35 at 34:57-36:16.. In order to ensure that Purdue and Rhodes's discovery is explicitly reflected in the claims, they also recite 8α as the source of at least a portion of the minimal amounts of 14-hydroxy remaining in the oxycodone API: "wherein at least a portion of the 14-hydroxy[] is derived from 8α" ('072 and '799 claims, A475-76 at 34:54-36:14 & A534-35 at 34:57-36:16) or "having an 8α component" ('800 claims, A504-06 at 34:22-38:53).

The inclusion of this "8α" language in the claims was directly related to proceedings in the PTO and before this Court regarding an earlier, related application ("Chapman"), never issued as a patent, which did not mention 8α in its claims. Instead, the earlier Chapman application's claims recited a process for preparing oxycodone with 14-hydroxy under conditions suitable to convert "8, 14-dihydroxy[]," without differentiating between the 8α and 8β forms of 8, 14-dihydroxy or in any way claiming Purdue and Rhodes's discovery of 8α. A98577-83. In an interference, the PTO declared the challenged claims invalid as obvious; this Court, over a dissent, affirmed, because "[t]he claim does not . . . differentiate between the 8α and 8β forms of 8, 14-dihydroxy," and the Chapman application "never claimed 8α as crucial to the invention before the Board." *Chapman v. Casner*, 315 F. App'x 294, 296 (Fed. Cir. 2009). The dissent would have permitted the claims to issue without reciting 8α, because the nonobvious discovery of 8α led to the invention. *Id.* at 298-300 (Rader, J., dissenting) (citing

and quoting *Eibel Process Co. v. Minnesota & Ontario Paper Co.*, 261 U.S. 45 (1923)). Nonetheless, the absence of 8α in the claims was determinative, because 8, 14-dihydroxy included 8β, and 8β was already disclosed in the prior art. *Chapman v. Casner*, 315 F. App'x at 296-97.

Consistent with the PTO and this Court's concerns, Purdue and Rhodes amended the claims of the low-ABUK patent applications to include the claims now on appeal. Unlike the method claims held obvious in *Chapman*, the product claims here expressly recite 8α as a source of the minimal amounts of 14-hydroxy in the salt. Further, Purdue and Rhodes explained that these claims were innovations because the prior art "fails to mention 8α[] at all, and therefore could not have suggested 'a dosage form comprising 14-hydroxy[] derived from 8α[],' as recited in these claims." A9528; A10370-72; A10701-04; *accord* A1795-98; A1802; A1813-14; A9526-28; A10602-12; A10701-04; A14203; A16822-24; A17087; A17675-77; A17924-28; A18178-88; A24152; A25216-26; A25308-12; A24554.

In 2010, the PTO allowed the claims, issuing the low-ABUK patents with the claims reciting 8α and the low impurity levels. A448-76; A477-506; A507-35; A16118; A23456; A30729. Purdue listed the low-ABUK patents in FDA's Orange Book for its original OxyContin® NDA, and again listed them for its reformulated OxyContin® NDA. A1182-83; A1219-21; A4835-37; A46015-16; A46020-21;

A46023; A46072-73.

C. The '383 Patent Claims an Abuse-Deterrence Formulation

Around the same time that Purdue and Rhodes were attempting to solve the 14-hydroxy problem, Purdue was also seeking to improve its OxyContin® product by making it more abuse-resistant. A73-74. The '383 patent provided a solution. Owned by Grünenthal and licensed to Purdue, the '383 patent relates to making drugs so hard and crush-resistant that they greatly deter abuse but still deliver controlled release of oxycodone.

Grünenthal and Purdue asserted claims 1, 2, 5, 7, and 8 of the '383 patent. Independent claim 1 recites "[a] thermoformed dosage form" including, among other ingredients, an active ingredient with "abuse potential (A) selected from the group consisting of opiates and opioids" and a polyalkylene oxide, "wherein said dosage form has a breaking strength of at least 500 N and wherein the active ingredient with abuse potential (A) is present in a controlled release matrix." A553 at 21:12-14. Independent claim 5 recites a process for making the product of claim 1. A553 at 22:3-8. Claims 2 and 8 depend from claim 1; claim 7 depends from claim 5. A553 at 21:2-22:17.

1. Purdue's Twin Goals of Effective Delivery and Deterring Abuse

By the time of the '383 patent, opioid abuse had been significantly increasing for the prior two decades, and had become a national health problem.

A2145; A2153-56. OxyContin® was a primary target. A85519-24; A85850-67.

For legitimate patients, OxyContin® was a critical and positive pain treatment. Its extended-release formulation, designed to deliver oxycodone over twelve hours, provides great relief to patients suffering chronic pain. A2156-57. In order to last over twelve hours, OxyContin® contains a large dose of oxycodone API, compared to formulations lasting only four to six hours. A2156-57.

OxyContin®'s amount of oxycodone, however, posed safety risks. So that it would release the oxycodone after ingestion, OxyContin® was originally formulated in a matrix that could easily be crushed. Unfortunately, abusers would crush the tablet to obtain a powder of oxycodone API that, when swallowed, snorted intranasally, or injected intravenously (after being mixed with water), would be released immediately and not gradually over time as intended. A2147-53; A2156-57; A2214-15; A85850-67. Original OxyContin®'s easy crushability was also a concern for legitimate patients, who might accidentally bite down on the tablet or, for those with difficulty swallowing, might cut or crush it. A2147. This would defeat the intended controlled-release properties and, instead, unintentionally expose the patient to the same opioid "high," and withdrawal issues, experienced by abusers. A2147; A2162-64; A2213-19.

A primary focus of abuse-deterrence research involved adding an antagonist, which would be activated if the tablet were crushed, thereby blocking the opioid's

effects. A2160-61; A85850-67. This approach, however, also risked diminishing the drug's efficacy for legitimate patients who bit into, crushed, or cut the tablets. A2161-63; A85850-67. Furthermore, the antagonist could leak within intact tablets, again blocking the drug's intended effects. A2217; A2234-35. Purdue and other oxycodone manufacturers needed a different solution that would deter abuse (or patient misuse), while simultaneously preserving the tablet's legitimate delivery of effective, extended-release pain relief.

2. The '383 Patent and Grünenthal's License to Purdue

The art viewed crush-resistance as incompatible with effective controlled-release drug delivery. Grünenthal, however, succeeded by combining these seemingly incompatible qualities into a crush-resistant, but still effective, controlled-release tablet. *See* Grünenthal Br. at 9-13. Ultimately, after much experimentation in the face of industry skepticism, Grünenthal developed an opioid tablet with sufficient breaking strength to withstand crushing and with the ability to deliver extended release. Specifically, the '383 patent claims the use of a thermoformed high-molecular-weight PEO formulation that makes the tablet extremely hard and therefore difficult to crush. A553 at 21:2-22:17; A554. Grünenthal applied for the '383 patent in 2003; it issued in February 2012. A537.

Believing that tablet hardness would interfere with releasing the API, Purdue and others in the field were skeptical. A2221-23; A83974-81; A87092-94.

Grünenthal's technology, however, proved effective, and Purdue took a license under several Grünenthal patent applications, including the then-pending '383 application. A2213-23; A2257-65; A2275-76; A2346-52; A2500-02; A5758-64; A85662; A85669-73; A85719; A85981-84; A87090-94; A87268-99. Purdue's license included the right to sue for infringement. A85695-97. Competitors, including Johnson & Johnson and Endo, likewise paid homage to Grünenthal's achievement by licensing the '383 patent for their own non-oxycodone products. A2533-45; A87365; A87464; A87471; A87492; A87566-68.

3. FDA Approval of the Reformulation, Purdue's Replacement of Original OxyContin® with the Reformulation, and FDA Approval of Abuse-Deterrent Labeling for the Reformulation

In 2007, Purdue filed a new NDA seeking FDA approval of its reformulated oxycodone product. A2226; A2244; A2264-74; A84873-84958. In 2012, Purdue amended the NDA to include the '383 patent. A153426-29. Although still using the same registered trademark OxyContin®, the reformulation is a different drug. "Reformulated OxyContin®" incorporates not only the low-ABUK patent technology introduced into original OxyContin® in 2005, but also novel abuse-deterrent technology, including Grünenthal's technology that later ripened into the '383 patent. FDA approved the NDA for Reformulated OxyContin® on April 5, 2010, and, in August 2010, Purdue stopped selling original OxyContin® entirely, and began selling Reformulated OxyContin®. A2314-22; A85068-85152. Annual

sales of Reformulated OxyContin® are approximately $2 billion. A2564-69; A2585-89; A88247.

Purdue's efforts toward a safer product did not end with approval of Reformulated OxyContin®. Purdue conducted numerous and extensive post-launch studies to evaluate the effectiveness of its new product in reducing abuse and its harmful consequences. The findings "indicate[d] that replacement of the original formulation of OxyContin with the reformulated version has resulted in a decrease in misuse and abuse." A85194-95; *see also* A2323-27; A85380-83; A85527-43; A85913-27. Those findings led FDA, on April 16, 2013, to issue an official decision that, due to the improved safety of Reformulated OxyContin® compared to the risks of original OxyContin®, original OxyContin® was withdrawn for reasons of safety. A85635-38. FDA acknowledged, in that same decision, that Reformulated OxyContin®, while providing the same therapeutic benefits as original OxyContin®, is more effective in deterring would-be abusers. A2325-27; A2561-63; A85153-86; A85608-43. Accordingly, FDA prohibited all generic manufacturers from selling generic versions of original OxyContin®. A85638; A85642-43. But for FDA's decision recognizing the medication's abuse-deterrent properties, Reformulated OxyContin® would have faced substantial competition from generic copies of the original formulation. A2595-96. Every sale of Reformulated OxyContin® is thus directly tied to the '383 patent.

Also on April 16, 2013, and based on Purdue's studies, FDA approved supplemental labeling for Reformulated OxyContin® that describes its abuse-deterrent properties, *i.e.*, that the reformulated product has physical and chemical properties expected to make abuse via injection or snorting difficult and therefore likely to reduce abuse. A2325-27; A2558-63; A85153-86; A85608-43. Reformulated OxyContin® is the first opioid product with FDA-approved abuse-deterrent labeling. Others have tried but failed to obtain abuse-deterrent labeling. A2169; A2596-99; A3771.

D. The District Court Proceedings

These cases arise under the Hatch-Waxman Act in response to Defendants' ANDAs seeking FDA approval to market generic versions of Reformulated OxyContin®. On March 23, 2011, Purdue sued Teva for infringement of the low-ABUK patents. A4727-35. On June 28, 2012, Purdue and Grünenthal jointly sued Teva for infringement of the '383 patent. A5648-72. Between November 2011 and January 2013, Purdue filed similar lawsuits against Epic, Mylan, and Amneal for infringement of the low-ABUK patents.[2] A5730-38; A5812-19; A6552-59. The two Teva cases were consolidated and joined with the Epic, Mylan, and Amneal cases in multi-district litigation for pretrial purposes. A614; A637-38;

[2] Another Grünenthal patent asserted against Teva and Amneal (the '314 patent) is not on appeal.

A669-70; A683; A695.

On August 23, 2013, the court construed the claims, determining, as relevant here, that the asserted claims of the '072 and '799 patents are product-by-process claims. A302-05. It is undisputed that the asserted claims of the '800 patent, which expressly claim compositions made by the process of either claim 1 or claim 57, *are* product-by-process claims. A55 n.6.

In September and October 2013, the court held a three-week bench trial in the Teva cases; the parties also adopted, as part of the record, the eight-day bench trial in 2012 from an earlier case involving solely the low-ABUK patents.[3] (That case involved different defendants, and it settled without a final judgment.) On January 14, 2014, the court entered its findings of fact and conclusions of law, holding that all of the claims on appeal are infringed by Teva's proposed generic product, but are invalid as anticipated (the '383 patent) or obvious (the low-ABUK and '383 patents). A61-64; A97. The court entered a parallel order of invalidity of

[3] For the low-ABUK patents, witnesses included defendants' experts Dr. Clayton Heathcock and Dr. Gary Molander; Purdue's expert Dr. James Wuest; named inventors Dr. Robert Kupper and Lonn Rider; Rhodes president Randy Shamblen; Dr. Karen James of Noramco; and Russell Gasdia and James Kelly of Purdue.

For the '383 patent, witnesses included Teva's expert Dr. Fernando Muzzio; Plaintiffs' experts Dr. Martyn Davies and Dr. Jerry Hausman; named inventor Dr. Johannes Bartholomäus; Purdue scientists Brianne Weingarten, Dr. Robert Kaiko, and Dr. Richard Mannion; Mr. Gasdia; and Dr. Feng Zhang, co-inventor of the McGinity application.

the low-ABUK patents in the Epic, Mylan, and Amneal cases. A8468-72.

SUMMARY OF ARGUMENT

In claiming oxycodone substantially free of 14-hydroxy, the asserted claims of the low-ABUK patents embrace an innovation never before created or contemplated in the art. The key was Purdue and Rhodes's discovery of the never-before-known 8α molecule and its particular, unique properties. The district court's legal errors lay principally in its failure to properly credit the discovery of 8α as the core of the claimed inventions, which led it to the erroneous conclusion that "the discovery of 8α [was] immaterial to the low-ABUK product claimed by the patents." A58. The discovery of 8α as the cause of the high-ABUK problem allowed Purdue and Rhodes to solve the problem. Under *Eibel Process* and this Court's case law, that solution—inextricably tied to the discovery of 8α's existence—was not obvious. Each judgment as to the '072, '799, and '800 patents should be reversed.

The judgment of invalidity of the '383 patent should also be reversed. As described in Grünenthal's brief, and elaborated below, the prior art did not anticipate or render obvious the '383 patent's solution to the vexing problem of deterring abuse while still allowing controlled release of oxycodone; the prior art lacks multiple limitations of the claims, and the court improperly used hindsight to evaluate the art. In addition, the court failed to credit the unique evidence

available in this case showing FDA's recognition of the '383 technology and its nexus to OxyContin®'s success. Particularly in the face of that real-world evidence, patent protection was appropriate.

STANDARDS OF REVIEW

Claim construction is reviewed *de novo*. *Lighting Ballast Control LLC v. Philips Elecs. N. Am. Corp.*, 744 F.3d 1272, 1276-77 (Feb. Cir. 2014) (en banc).

Obviousness is a question of law reviewed *de novo*, and the underlying factual findings—(1) the scope and content of the prior art; (2) the differences between the prior art and the claims at issue; (3) the level of ordinary skill in the art at the time the invention was made; and (4) objective evidence of nonobviousness—are reviewed for clear error. *Power-One, Inc. v. Artesyn Techs., Inc.*, 599 F.3d 1343, 1351 (Fed. Cir. 2010). Anticipation is a question of fact reviewed for clear error. *Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075, 1082 (Fed. Cir. 2008). Patents are "presumed valid," 35 U.S.C. § 282, and the defendant must prove invalidity by clear and convincing evidence. *Microsoft Corp. v. i4i Ltd. P'ship*, 131 S. Ct. 2238, 2242 (2011).

ARGUMENT

I. THE CLAIMS OF THE '072, '799, AND '800 PATENTS WERE NONOBVIOUS

A patent claim can be held obvious only "if the differences between the claimed invention and the prior art are such that the claimed invention as a whole

would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains." 35 U.S.C. § 103. In this case, the correct law, applied to the district court's own factual findings, establishes that the claims were nonobvious. In holding otherwise, the court made three principal errors. *First*, it ignored as "immaterial" Purdue and Rhodes's discovery of 8α and its properties, without which oxycodone API with low 14-hydroxy levels could not have been invented, *see Eibel Process Co. v. Minnesota & Ontario Paper Co.*, 261 U.S. 45, 68 (1923). *Second*, it construed and applied the claims as though the 8α limitations did not exist. *Third*, it ignored or misunderstood the role of objective evidence, extensive on this record, of nonobviousness.

A. Due To The Discovery Of 8α As The Source Of The Problem, The Claims Were Nonobvious

As the district court correctly found, two aspects of the claimed low-ABUK inventions "principally distinguish the prior art from the patents-in-suit and the asserted claims." A44. *First*, "the prior art did not disclose oxycodone API substantially free of 14-hydroxy." A45. *Second,* "the prior art did not disclose the existence of 8α or teach that it converts to 14-hydroxy"—rather, Purdue and Rhodes "discovered 8α as the source of the 14-hydroxy problem." A26; A44. These differences are inextricably related: Low-ABUK oxycodone API was completely unknown in the prior art *because* 8α was unknown—until Purdue and

Rhodes scientists discovered 8α and its unique properties, which created high levels of 14-hydroxy in oxycodone API. As such, the claims are drawn to a new and nonobvious invention—oxycodone API with low levels of a potentially genotoxic impurity. The claims are nonobvious as a matter of law, based on the district court's own factual findings.

1. Products With Low Levels Of 14-Hydroxy, "Derived From 8α," Were Not Known In The Prior Art

The claims in suit recite never-before-created oxycodone products in which the 14-hydroxy in the oxycodone is (1) present at very low levels (*e.g.*, "substantially free of 14-hydroxy"), and (2) "derived," at least in part, from the newly discovered 8α (or, as in the '800 patent, "having" the newly discovered 8α as a precursor component to 14-hydroxy). As the district court found, these limitations were not in the prior art. A45-46.

As to the "substantially free of 14-hydroxy" (and related) limitations, the district court found that "the prior art did not disclose oxycodone API substantially free of 14-hydroxy." A45. Prior to the invention of the low-ABUK patents, the best the industry had been able to accomplish was oxycodone API having "levels of 14-hydroxy at rates greater than 800 ppm." A45. The asserted low-ABUK claims, however, claim oxycodone API having "less than 25 ppm" ('799 patent) or less than 25, 15, or 10 ppm ('072 patent) of that impurity, or oxycodone salt

"substantially free of" or having less than about 25, 15, or 10 ppm of that impurity ('800 patent).

This represented a major advance over the prior art. Despite the "impressive" level of ordinary skill in the art (A39), the industry's longstanding effort to reduce the levels of 14-hydroxy (A23), an industry "motivated to produce low-ABUK oxycodone . . . for some time" (A56), and FDA's insistence on reduced 14-hydroxy levels (A56), the pharmaceutical industry had repeatedly failed to achieve such reductions until Purdue and Rhodes scientists discovered that the source of this problem was the never-before-known 8α molecule.

As to the "derived from 8α" limitations, the district court's findings again make the case: "the prior art did not disclose the existence of 8α or teach that it converts to 14-hydroxy" (A44); "its very existence was unexpected" (A50); and it was not known until "Rhodes research scientist Lonn Rider hypothesized" the existence of 8α in 2002 (A24), leading Rhodes and Purdue to "investigate[]" and, eventually, discover the existence of 8α and confirm its role in the formation of 14-hydroxy. A25. That was the key to enabling Purdue and Rhodes to finally solve the problem and create—for the first time—"oxycodone API with 14-hydroxy levels less than 10 ppm." A27; *see generally* A27-31; A44-45.

2. The Low Levels Of 14-Hydroxy In The Claimed Products Demonstrate Nonobviousness

The asserted claims of the '072, '799, and '800 patents were not obvious at

the time of the inventions, because each claim requires low levels of 14-hydroxy that had never before been suggested in the prior art, and were not then obviously achievable.

The district court's own findings make this case. The prior art did not disclose low-ABUK oxycodone salt; rather, it disclosed oxycodone salt "with 14-hydroxy at rates greater than *800 ppm*." A45 (distinguishing Ramanathan and Chiu); A3284-93; A99580-90; A147979-83. Because the prior art did not know 8α at all (and thus did not include 8α-derived 14-hydroxy), it could not teach or suggest that 8α formed new 14-hydroxy, and could not teach or suggest a solution to the high-ABUK problem. The prior art provided no teaching or suggestion to hydrogenate as part of the salting step (step 3). Instead, the prior art misdirected those skilled in the art to extend the hydrogenation (step 2) that converted the thebaine-derived 14-hydroxy to free base, as Purdue and Rhodes first tried. A821-22; A826-33; A1207-10; A1984-88; A41017; A42322-27; A45502-06. Further, even if hydrogenation were run again in conjunction with step 3, without knowing about 8α to inform the use of particular reaction conditions (time, acid amount, etc.), a cycle of continuing creation of 14-hydroxy would have ensued, and it would not have been obvious how to stop it. A2011-14. In fact, Purdue and Rhodes experienced this, until they knew how to specifically account for 8α. *See* pages 18-20, above.

Prior to the discovery of 8α and the new 14-hydroxy that it created, a person of ordinary skill would not have considered, let alone tried, Purdue and Rhodes's solution—hydrogenation of the oxycodone salt, under conditions that accounted for 8α's sensitivity to acid—because no one understood the different reaction that formed the new 14-hydroxy. Only with improper hindsight knowledge of 8α, its properties, and new 8α-derived 14-hydroxy, was the district court able to reach the conclusion that it would have been obvious to try a second, later hydrogenation. *See Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1354 (Fed. Cir. 2013) ("Only after recognizing the existence of the problem would an artisan *then* turn to the prior art and attempt to develop [the claimed solution].") (emphasis in original).

The Chiu patent and Proksa article demonstrate the prior art's failure to disclose or even suggest Purdue and Rhodes's solution. A99576-77; A99580-90. Each reference was directed to lowering 14-hydroxy levels in oxycodone *free base*, not in the API or salt as required by the low-ABUK patent claims. A30; A42. Chiu also disclosed adding acid before, during, and after the hydrogenation that formed the free base, likely creating more, not reducing, 14-hydroxy. A58 (district court noting that "Purdue's solution" differed from the prior art, especially Chiu, because of its attention to hydrogenating the salt form and doing so in a different way). The district court expressly found this: "Ironically and unbeknownst to Chiu, he likely converted latent 8α into 14-hydroxy when he added acetic acid."

A45 (citing A2012-14; A4391-93; A99580-90). Thus, both Chiu and Proksa affirmatively taught away from the low-ABUK patents' inventions. This sort of "divergent" solution demonstrates nonobviousness. *See In re Kubin*, 561 F.3d 1351, 1357 (Fed. Cir. 2009).

3. Purdue And Rhodes's Discovery Of 8α Demonstrates Nonobviousness

Because of Purdue and Rhodes's discovery of 8α—the key that unlocked the door to reducing levels of 14-hydroxy in oxycodone API and salt—the claims of the low-ABUK patents are nonobvious under *Eibel Process Co. v. Minnesota & Ontario Paper Co.*, 261 U.S. 45 (1923). Under *Eibel Process*, where an inventor discovers a nonobvious source of a problem and then applies a remedy in response, the invention is nonobvious and worthy of a patent—even if the remedy, standing alone, would generally appear to be known in the art. Purdue and Rhodes's discovery of 8α, 8α's conversion to 14-hydroxy during the salting step (step 3), and the solution to the problem based on those findings, demonstrate nonobviousness under *Eibel Process*. The court's failure to apply *Eibel Process* was legal error.

The *Eibel Process* patent involved an improvement to a paper-making machine. At the time, paper-making machines could operate only so fast; otherwise, they produced wrinkled paper. 261 U.S. at 54. Eibel's patent called for increasing the pitch (angle) of the wire of the machine and thereby, through gravity, causing the paper stock to travel at substantially the same speed as the wire. *Id.* at

49. As a result, Eibel's machine produced, at speeds higher than that of the prior art, "a strong, even and well-formed sheet which is more uniform than usual." *Id.* Eibel sued an infringer. The Supreme Court, speaking through Chief Justice Taft, rejected the infringer's obviousness defense, cautioning that one "must not lose sight of the fact that one essential part of Eibel's discovery was" determining "the trouble causing the defective paper product under high machine speed"—*i.e.*, Eibel determined "the causal connection between the unequal speeds of the stock and the wire, and the disturbance and rippling of the stock, and between the latter and the defective quality of the stock." *Id.* at 68. Although Eibel applied a well-known force—gravity—to solve this problem, the basis of the invention was his discovery of the ***source*** of the problem, and his subsequent application of a remedy to that problem. *Id.* "[W]hat he saw and did was not obvious and *did* involve discovery and invention." *Id.*[4]

Eibel Process carries out the Patent Act's mandate to evaluate obviousness by viewing the claimed invention "as a whole." 35 U.S.C. § 103; *In re Kaslow*, 707 F.2d 1366, 1373 (Fed. Cir. 1983). This includes "the discovery of the source

[4] The Court elaborated: "We cannot agree with the Circuit Court of Appeals that the causal connection between the unequal speeds and the wire, and the disturbance and rippling of the stock, and between the latter and the defective quality of the paper in high speeds of the machine, was so obvious that perception of it did not involve discovery which will support a patent." *Id.*

of persistent trouble despite the teachings of the prior art." *In re Aufhauser*, 399 F.2d 275, 277 (C.C.P.A. 1968). As this Court has put it, "an invention can often be the recognition of a problem itself." *Leo Pharm.*, 726 F.3d at 1353; *see also In re Sponnoble*, 405 F.2d 578, 585 (C.C.P.A. 1969) (reversing claim rejection where applicant "discovered the source of the problem"). Thus, when invention lies in the discovery of the cause of a problem, "the determinative question [under § 103] is whether that cause would have been recognized by one of ordinary skill in the art at the time the invention was made." *In re Peehs*, 612 F.2d 1287, 1290 (C.C.P.A. 1980) ("find[ing] no support for the conclusion that those of ordinary skill in the art would have recognized" the source of the problem); *In re Conover*, 304 F.2d 680, 684 (C.C.P.A. 1962) ("The rationale of the Eibel case requires that we consider the unobvious cause of the problem solved, as well as the solution proposed, in arriving at a final determination of whether the invention claimed is 'obvious' within the meaning of section 103.").

The district court's own findings answer the "determinative question" framed by *In re Peehs*—whether an ordinarily skilled artisan would have recognized the cause of the problem at the time of the invention—with a resounding "no." In the district court's words, "8α [w]as the source of the 14-hydroxy problem," but it "was unknown in the prior art; its very existence was unexpected." A26; A50. As the patents disclose, Purdue and Rhodes discovered

that the 14-hydroxy appearing in the salt was not carried over from the hydrogenation step, but was new 14-hydroxy derived from the previously unknown and "unexpected" 8α, and that 8α was reacting with the acid in the salting step to create the problematic, new 14-hydroxy. A455. This discovery was critical to the inventors' solution of adding a second hydrogenation step tailored to 8α to convert new 14-hydroxy and avoid creating even more of it.

Not knowing the source of the problem, ordinarily skilled artisans could not have solved the problem. Indeed, without any knowledge of 8α, the art misdirected its efforts at the thebaine-derived 14-hydroxy, which—it turned out—was a fool's errand. Unlike an invention "borne of common sense and guided by routine experimentation" (A56), here, neither the underlying problem nor consequent solution were obvious. As the *Chapman* dissent stated, Purdue and Rhodes's discovery of 8α, which led to their "important and innovative solution," "calls to mind the Supreme Court's resolution of *Eibel Process*." *Chapman*, 315 F. App'x at 298 (Rader, J., dissenting).

Consistent with *Chapman*'s guidance, Purdue and Rhodes explicitly claimed both the 8α solution and the lower impurity levels in the '072, '799, and '800 patents. Accordingly, these claims should have been upheld by the district court. However, even though Purdue consistently raised this *Eibel Process* argument, the district court did not even mention it. A3934-40; A4914.16; A5359-60; A7315;

A7483-84.

The district court instead focused on the level of difficulty of the solution *once* 8α was discovered: "[T]he inventors' knowledge of 8α defined a universe of possible 8α-specific processes to achieve low-ABUK oxycodone." A59. That flawed reasoning improperly assumed into the prior art knowledge of the single most critical part of the claimed invention—the "unexpected" discovery of 8α and its properties—contrary to *Eibel Process*: "The discovery of the source not known before and the application of the remedy" constitute patentable invention. 261 U.S. at 68. The district court's focus should have been on the discovery of the *source* of the problem, not the purported ease of devising the solution once the source was uncovered. *See, e.g.*, *In re Aufhauser*, 399 F.2d at 277 ("The strength (as well as an apparent weakness) of appellant's case is found in the relatively simple technical difference between his invention and the prior art," but because this difference "solved a problem," the claim was allowed).

B. The District Court Improperly Disregarded The "Derived From 8α" And Similar Limitations For Purposes Of Determining Validity

Apart from its failure to address Purdue's *Eibel Process* argument, the district court erred by holding, "[a]s a matter of law," that in evaluating the nonobviousness of the claims, "the discovery of 8α [is] immaterial," such that "the 8α-derived limitation of the asserted product claims is disregarded as a process

limitation." A55. This error—which, like the court's failure to consider the discovery of 8α and its unique qualities as part of the patentable invention under *Eibel Process*—was premised on the court's twin, erroneous views that (i) "derived from 8α" is a process limitation, and (ii) this Court's precedent requires "the validity of a [product] claim [to be] assessed without reference to the claim's process limitations." A302 at n.10 (citing *Greenliant Sys., Inc. v. Xicor LLC*, 692 F.3d 1261, 1268 (Fed. Cir. 2012)). "Derived from 8α" is not a process limitation, and even if it were, this Court's precedents do not give license to entirely "disregard" limitations—even supposedly "process" or "source" limitations—as "immaterial" to the nonobviousness analysis. That is particularly true where, as here, the product claimed—low-ABUK oxycodone API—is a new product. The additional "derived from 8α" limitation nonetheless imposes a structural limitation that further demonstrates the claims' nonobviousness, and honors this Court's decision in *Chapman v. Casner*, which upheld the Board's obviousness holding (as to different but related claims) on the ground that the Chapman claims did not "differentiate between the 8α and 8β forms of 8, 14-dihydroxy." 315 F. App'x at 296-97.

1. "Derived from 8α" is not a process limitation. The "default" rule is that limitations in product claims are "structural" limitations, not "process" limitations. *Gemtron Corp. v. Saint-Gobain Corp.*, 572 F.3d 1371, 1379 (Fed. Cir.

2009) ("even words of limitation that can connote with equal force a structural characteristic of the product or a process of manufacture are commonly and by default interpreted in their structural sense" (quoting *3M Innovative Props. Co. v. Avery Dennison Corp.*, 350 F.3d 1365, 1371 (Fed. Cir. 2003))). That rule applies here. The claims of the 072 and '799 patents do not use the term "process," and neither the court nor Defendants identified any precedent construing "derived from" as a process limitation. It is not.

Cases considering whether "derived from" represents a process limitation are few, but they uniformly support Purdue's position. In *Ex Parte Berkman*, 90 U.S.P.Q. 398 (B.P.A.I. 1950), the Board held that a claim reciting material "derived from plants" was an "extremely broad claim to an active *material* derived from plants." *Id.* at 400. Only claims reciting material derived from a substance "by a process" having specific, enumerated steps were "more limited" to products "derived from . . . material ***by a process***"—*i.e.*, product-by-process claims. *Id.* And in *Kemin Foods, L.C. v. Pigmentos Vegetales Del Centro S.A.*, 301 F. Supp. 2d 970 (S.D. Iowa 2004), *modified in part on other grounds*, 319 F. Supp. 2d 939 (S.D. Iowa 2004), the district court held that the claim limitation "derived from plant extracts" was "a claim to a composition, contrary to PIVEG's suggestion that the composition claims of the '714 patent are product-by-process claims." *Id.* at 983-84. Just as "derived from plants" and "derived from plant extracts" are

structural, product limitations, "derived from 8α" is likewise a structural, product limitation—not a process limitation.

This stands in sharp contrast to the admittedly process limitations of the '800 patent. For example, claim 30 of the '800 patent covers "Oxycodone salt prepared according to the process of claim 1." A505 at 35:49-50. All agree that this is a product-by-process claim, because it expressly incorporates the specific process steps of claim 1. A504 at 34:22-35. The '800 patent was prosecuted and issued at the same time as the '072 and '799 patents. The very different wording of the '072 and '799 patent claims—"derived from 8α"—is a powerful indicator of different meaning and different scope. *See Andersen Corp. v. Fiber Composites, L.L.C.*, 474 F.3d 1361, 1369-70 (Fed. Cir. 2007).

Finally, the prosecution history of the '072 and '799 patents shows that "derived from 8α" denotes structure, not process, because the 8α limitation brought further structural definition to the claimed product consistent with *Chapman*. That Chapman application, to which the low-ABUK patents are related, was rejected because it did not recite 8α—instead it recited "8,14-dihydroxy-7,8-dihydrocodeinone," *i.e.*, 8,14-dihydroxy generic to 8α or 8β, without further reciting or claiming Purdue and Rhodes's discovery of 8α. A10587-88; *Chapman v. Casner*, 315 F. App'x at 296-97. The '072 and '799 claims (as well as the '800 claims) filled this gap by expressly reciting 8α in addition to the novel and

nonobvious low-ABUK levels. The inventors distinguished the claims of the '072 and '799 patents based on 8α, pointing out that neither Chiu, nor Proksa, nor Weiss mentioned 8α or compared its structure to 8β. A9526-28; A10370-72; A10701-05; A24152; A25308-12; A99572-77; A99580-90; *see also* A16822-24; A17675-77; A17924-28 ('800 patent). Based on these arguments, the claims were allowed. A16118; A30729.

The district court thought it had found support for its ruling in parts of the specification that discuss "process conditions under which acidifying oxycodone free base will cause 8α to convert into 14-hydroxy." A303-04 (citing Figure 2 and Example 3). But that impermissibly "import[ed] process limitations from the specification into the claims." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1323 (Fed. Cir. 2005). Of course, the specification—common to all three low-ABUK patents—contains "a written description . . . of the manner *and process* of making and using" the invention, 35 U.S.C. § 112(a) (emphasis added), and it supports the '800 patent, which (unlike the '072 and '799 patents) is replete with process claims. *See Amgen Inc. v. F. Hoffmann-LaRoche, Ltd.*, 580 F.3d 1340, 1348-49 (Fed. Cir. 2009) ("product" and "process" patents shared the same specification). It was thus appropriate for the specification to reference processes, but those processes may not be engrafted onto the '072 and '799 claims as unwritten process limitations.

2. Even if "derived from 8α" and the similar "8α component" term in the '800 patent were viewed as process limitations, they cannot be entirely ignored as "immaterial." The district court's nonobviousness analysis derailed when it held that it was required to "disregard" the 8α limitations entirely (A58), and assess the low-ABUK claims' validity "*without reference to the claim's process limitations*." A302 at n.10; *see also* A20 (same).

The district court cited *In re Thorpe*, 777 F.2d 695, 697 (Fed. Cir. 1985), a case arising from the PTO, for the proposition that the court was required to disregard the 8α limitations as process limitations having "no patentable significance." A55; *see also* A20 (citing *Greenliant Systems*, 692 F.3d at 1268); A58 (citing *SmithKline Beecham Corp. v. Apotex Corp.*, 439 F.3d 1312, 1316-17 (Fed. Cir. 2006)). But none of those cases so holds. In fact, this Court's decisions have repeatedly commanded that process limitations should be considered, even though the "focus" in the invalidity analysis "is on the product and not the process of making it." *Amgen*, 580 F.3d at 1369-70 (citing *Atlantic Thermoplastics Co. v. Faytex Corp.*, 970 F.2d 834, 841 (Fed. Cir. 1992), and *Abbott Labs. v. Sandoz, Inc.*, 566 F.3d 1282, 1293 (Fed. Cir. 2009) (en banc)).

The Court's product-by-process jurisprudence speaks in terms of giving "*less regard* for the process limits," but not to the extent of complete "disregard" or "immateriality." *Compare Atl. Thermoplastics*, 970 F.2d at 841 ("less regard"),

with A58 ("the 8α-derived limitation of the asserted product claims is *disregarded* as a process limitation"). This is because of the "long-standing rule that an old product is not patentable even if it is made by a new process." *Amgen*, 580 F.3d at 1370. Where the new and old products are identical, no "process" limitation can save a later patent claiming the same product made by a different process; the same result would follow where the process yields only an obvious variant on the old product. (Indeed, in *Thorpe*, "Thorpe d[id] not assert that the product of his process is different from the product of the prior art." 777 F.2d at 697.) But, where a process imparts "structural and functional differences" that make the claimed product different from the prior art, a process limitation may be relevant, and that is so even if that limitation is "not explicitly part of the claim." *Amgen*, 580 F.3d at 1370; *id.* at 1367 (production of erythropoietin (EPO) by recombinant process yielded EPO having "a higher molecular weight and different charge than urinary[-process] EPO due to differences in carbohydrate composition"); *see also SmithKline*, 439 F.3d at 1319 ("If those product-by-process claims produced a different product than that disclosed by the [prior art], there would be an argument that the [prior art] disclosure did not anticipate." (citing *In re Luck*, 476 F.2d 650, 653 (C.C.P.A. 1973) (same for obviousness)); Manual of Patent Examining Procedure § 2113 (9th ed. 2014).

That is the case here. The "8α" limitations—whether considered process, source, or structural limitations—contribute to defining the structure of the new and nonobvious product claimed in the low-ABUK patents: oxycodone API and salt substantially free of 14-hydroxy. The district court found that this product was new (A45), and that Purdue and Rhodes's discovery of 8α was a nonobvious, "unexpected" discovery (A50) that led to this product. A44. The combination of those findings should have led the district court to a holding of nonobviousness, but it did not.

3. The district court's view that 8α is "immaterial" led to its erroneous obviousness holding. By misreading this Court's precedents as requiring total disregard of the 8α limitation, the district court improperly eliminated from its nonobviousness analysis the significant inventive contributions of the low-ABUK patents. 8α, which was the reason that 14-hydroxy levels could not be minimized previously, "was unknown in the prior art; its very existence was unexpected." A50. Similarly flawed was the court's conclusion, "as a matter of fact," that "identification of a source of the 14-hydroxy in the end product does not have any effect on the structure or nature of the end product," because "[o]ne molecule of 14-hydroxy is the same as the next, whether derived from 8α or 8β." A58. While it is true that 14-hydroxy (the impurity) is the same molecule whether derived from 8α or elsewhere, the invention was not 14-hydroxy, but a new

oxycodone salt in which that potentially genotoxic impurity has been reduced to minimal levels. The court fundamentally misunderstood that the newly discovered 8α isomer, and its newly discovered, unique properties, were critical to achieving the substantially ABUK-free oxycodone API and salt claimed in the patents.

The court likewise erred by holding that "Purdue's low-ABUK process hinges on hydrogenation—not on 8α." A59. According to the court, the known use of hydrogenation to convert 14-hydroxy rendered the claims obvious, because the only "challenge facing the art [was] to decide where in the synthetic scheme to add hydrogenation." A59. The court relied on Dr. Heathcock's opinion that, if 100 college-level chemistry students were asked how to solve the "problem" of 14-hydroxy in oxycodone, "all 100 students would come up with the same answer: Hydrogenation." A57 (citing A1864). But, of course, "hydrogenation" by itself was not the answer. These hypothetical students also would have had to know the source of the 14-hydroxy, which was necessary to know when in the reaction process to perform the hydrogenation, and under what conditions. Dr. Heathcock assumed away the students' need to know the source of the problem (8α). Under that same logic, Eibel's paper-making machine would have been obvious because gravity, like hydrogenation, was commonly known.

Furthermore, the asserted low-ABUK claims are to products, not to "Purdue's low-ABUK process" (A59). And, by focusing on the steps taken once

8α and its properties were discovered, the court assumed away the major innovation of the low-ABUK patents—the discovery of a new and unexpected molecule, 8α, that was the culprit preventing anyone from creating low-ABUK oxycodone API. Hydrogenation was part of getting to the claimed invention—low-ABUK oxycodone API or salt—but the claimed invention is *not* hydrogenation. Indeed, the claims do not even mention hydrogenation. Without knowledge of 8α as the source of the new 14-hydroxy, the claimed invention was not possible. The discovery of 8α and its characteristics led to the "'unexpected results'" of the nonobvious composition ultimately claimed. A30-31; A1998-2005; A10701-04; A14203; A148307-10. What Dr. Heathcock missed is that knowledge of "hydrogenation" alone would cause his 100 students to simply repeat the prior art, like Purdue and Rhodes initially did; absent the knowledge of 8α and new 14-hydroxy, his students could not have solved the problem. That is why scientists of extraordinary skill, employed by pharmaceutical companies with a compelling desire and motivation to solve the problem of high-ABUK oxycodone API, repeatedly failed in their efforts. Until, that is, Purdue and Rhodes made their remarkable discovery.

C. The Objective Evidence Confirms Nonobviousness

The district court also erred by not addressing much of Purdue's objective evidence of nonobviousness, to which the court devoted only two pages of

reasoning. A61-62. And, as to the evidence the court did consider and reject, its reasons for doing so were unfounded—and often contrary to its own factual findings.

This Court's precedent "clearly hold[s] that secondary considerations, when present, must be considered in determining obviousness." *Ruiz v. A.B. Chance Co.*, 234 F.3d 654, 667 (Fed. Cir. 2000). Further, the scope of those factors is broad: "*Graham* set forth a *broad inquiry* and invited courts, where appropriate, to look at *any* secondary considerations that would prove instructive." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 415 (2007).

Objective indicia of nonobviousness do not serve merely as a check on a presumptive conclusion of obviousness, as the district court assumed. A61. This Court "has emphasized that consideration of the objective indicia is part of the whole obviousness analysis, not just an afterthought." *Leo Pharm.*, 726 F.3d at 1357; *see also In re Cyclobenzaprine*, 676 F.3d 1063, 1079-80 (Fed. Cir. 2012); *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1364-65 (Fed. Cir. 2008).

Premature conclusions of obviousness are not inconsequential. Objective indicia "can be the most probative evidence of nonobviousness in the record, and enables . . . the court to avert the trap of hindsight." *Crocs, Inc. v. Int'l Trade Comm'n*, 598 F.3d 1294, 1310 (Fed. Cir. 2010) (quoting *Custom Accessories, Inc.*

v. Jeffrey-Allan Indus., Inc., 807 F.2d 955, 960 (Fed. Cir. 1986)). They "lend a helping hand to the judiciary" in "discharg[ing] the technological duties cast upon it by patent legislation" and "resist[ing] the temptation to read into the prior art the teachings of the invention in issue." *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 36 (1966). Aptly labeled "objective evidence of innovation," such evidence allows the use of common sense, inquiring into "the manner in which the industry and the marketplace responded to the disclosure in a patent." *Apple Inc. v. Int'l Trade Comm'n*, 725 F.3d 1356, 1375 (Fed. Cir. 2013) (Reyna, J., concurring); *accord Demaco Corp. v. F. Von Langsdorff Licensing, Ltd.*, 851 F.2d 1387, 1391 (Fed. Cir. 1988) (objective indicia show "how the patented device is viewed in the marketplace, by those directly interested in the product"). Thus, premature conclusions of obviousness improperly invite the court to minimize or ignore objective indicia, which are meant to ensure that the judiciary, likely not versed in the technicalities of the art, fully appreciates the inventive contribution. Otherwise, a court could erroneously "construct a selective version of" the objective evidence "so as to confirm its [incorrect] hunch that the asserted claims were obvious." *In re Cyclobenzaprine*, 676 F.3d at 1079-80.

Here, while a proper understanding of the science and state of the art alone demonstrate the innovation and compel reversal, the easily accessible objective evidence overwhelmingly proves that the low-ABUK patents are nonobvious. One

important indicator is **the failure of others**. *See id.* at 1082. FDA's industry-wide push for lower 14-hydroxy levels began at the end of 2003. A41007-09; A42364-66. As the regulatory gatekeeper, FDA pronouncements—even if just suggestive—must be taken seriously. If suggestion becomes mandate, the consequences of failure are substantial—storehouses of product cannot be sold or used, and entire factories may be closed. A781-82. In this instance, however, FDA did not provide any indication of *how* manufacturers could meet its requirements or recommendations, and the industry stumbled and fell before Purdue and Rhodes identified the real problem and provided a solution. A1268-79. Even then, competitors tried and failed for several *more* years—ultimately copying Purdue and Rhodes's inventions. Teva's own API supplier, Noramco, was unable to obtain low ABUK levels until 2007, after Purdue and Rhodes's discovery of 8α, and the publication of a priority application—and it only did so by infringing the low-ABUK patents. A34-39; A49.

The district court found all of these facts, but failed to apply them to nonobviousness. That was legal error. Its conclusion that "no manufacturer made low-ABUK oxycodone until the FDA required it" (A62) was true as far as it goes, but it does not account for the court's related findings that the industry could not find a solution to the high-ABUK problem until *years* after Purdue and Rhodes discovered 8α and disclosed it in their patent applications. A33-39. As in *Eibel*

Process, 261 U.S. at 68, "[t]he fact that no one had applied a remedy for the consequent trouble until Eibel, and the final fact that when he made known his discovery, all adopted his remedy, leave no doubt in our minds that what he saw and did was not obvious and did involve discovery and invention." Likewise, the district court's view that nothing showed that Noramco "had been trying and failing to" develop low-ABUK oxycodone (A61) is directly contrary to the record. A3388; A41016-29; A47138.

Indeed, Noramco expressly credited Purdue and Rhodes with the discovery of 8α. Such **praise from competitors** "tends to 'indicat[e] that the invention was not obvious.'" *Power-One,* 599 F.3d at 1352 (citation omitted); *see also Gambro Lundia AB v. Baxter Healthcare Corp.*, 110 F.3d 1573, 1579-80 (Fed. Cir. 1997) (accused infringer's "recognition of the importance of this advance is relevant to a determination of nonobviousness"); *Minnesota Mining & Mfg. Co. v. Johnson & Johnson Orthopaedics, Inc.*, 976 F.2d 1559, 1575 (Fed. Cir. 1992) ("real world considerations," such as competitors' acknowledgement of the patented invention and its acceptance by the market, "provide a colorful picture of the state of the art, what was known by those in the art, and a solid evidentiary foundation on which to rest a nonobviousness determination"). In its application, Noramco recognized that the discovery of 8α as described in the '072, '799, and '800 patents was a major contribution to the field of developing low-ABUK oxycodone. A40851 at

3:60-63, 4:48-49, 4:54-61; *see also* A1295; A1300-02; A1627; A3388; A3982-83; A4072-73; A4231; A47137-38. And, the district court found that Noramco's patent "amounts to recognition in the industry" that Purdue and Rhodes discovered 8α. A51. With one of Defendants' own oxycodone suppliers unable to obtain low levels without Purdue and Rhodes's discovery, the low-ABUK patents could not have obvious.

The court also clearly erred when it dismissed evidence of **a long-felt but unmet need** because "FDA established a low-ABUK target" in 2003. A62. That finding is clearly erroneous, in multiple respects. What FDA did in 2003 was change the long-felt need into a *regulatory imperative* for low-ABUK oxycodone API. Long before FDA established its target, ABUKs were suspected of being genotoxic. A825-26. And even with its demand in 2003, FDA did not provide any guidance about *how* to achieve safer levels of 14-hydroxy. A780-84.

The court also denied the existence of a long-felt need by characterizing Purdue and Rhodes's inventive conduct as "prompt[]" and "swift[]" relative to FDA's 2003 pronouncement, emphasizing that the level of ordinary skill was "impressive." A46-51; A61-62. But in counting days or years to fault Purdue and Rhodes for their sophistication and inventiveness in solving the problem, the court violated Congress's directive that "[p]atentability shall not be negated by the manner in which the invention was made." 35 U.S.C. § 103. Further, the court

contradicted its own finding that "Rhodes had begun experimenting with ways to reduce 14-hydroxy levels in its oxycodone hydrochloride ***years before***" FDA required lower levels from Rhodes. A23 (citing A827-30). More to the point, the court's conclusion was blind to the unvarnished fact that, even possessing such impressive skills, ordinary artisans and incentivized competitors armed with their own skilled scientists failed to solve the low-ABUK problem before Purdue and Rhodes's discovery and disclosure of 8α. Tellingly, Teva's supplier Noramco could not even find a solution without **copying** Purdue and Rhodes's disclosure. A51. *See Ruiz*, 234 F.3d at 662-63 (copying is objective evidence of nonobviousness).

In other areas, the court misunderstood the evidence and its role in showing nonobviousness, particularly with respect to **commercial success**. *See Leo Pharm.*, 726 F.3d at 1358. Innovative pharmaceutical products such as OxyContin® undergo lengthy FDA review, as well as regulation within the Hatch-Waxman framework permitting competition from generic versions that, not having invested in the research and development, can be produced more cheaply. In that context, products are not subject to normal free-market forces that would allow a garden-variety economic analysis. Purdue and Rhodes's safety improvement overcame all of the regulator's concerns (A784-93; A1216-18; A45511-12), and FDA approved Rhodes as an oxycodone supplier.

The court, however, found that "[n]o commercial success can be attributed to the low-ABUK oxycodone API as *Purdue* had never marketed OxyContin® on the basis of its low-ABUK features." A61; *see also* A47-48. This inquiry was too narrow. It failed to evaluate *Rhodes's* commercial success. It was Rhodes that marketed the low-ABUK features of its oxycodone *to Purdue*—resulting in Rhodes satisfying FDA's requirements and becoming a viable oxycodone supplier to its customer, Purdue. A798. Only with that approval was Rhodes, based on the patented invention, able to garner a principal share of Purdue's oxycodone purchases. Since 2005, Rhodes's sales of oxycodone covered by the low-ABUK patents have been substantial—almost $71 million to Purdue in 2010 alone. A797; A45359; A45518. Without approval at FDA's mandated low-ABUK level, Rhodes would not have enjoyed success, or even been a viable oxycodone supplier—its ability to market and sell oxycodone API depended on its ability to make low-ABUK oxycodone. A715; A782-83. These facts establish nexus between the low-ABUK patents and Rhodes's commercial success.

In addition, the court failed to appreciate the regulatory context in which to evaluate *Purdue's* commercial success. If Rhodes had been unable to supply low-ABUK oxycodone, Purdue would have had *none*, given that its other supplier, Noramco, solved the problem only after having the benefit of Rhodes's work discovering 8α. Thus, while Rhodes's sales of low-ABUK oxycodone and

Purdue's sales of low-ABUK OxyContin® may not have increased relative to sales of predecessor high-ABUK products, *any* profit made as a result of low-ABUK OxyContin® should have been considered in the evaluation of commercial success—Rhodes's achievement was a but-for cause of Purdue's ability to reformulate original OxyContin® as a low-ABUK formulation. Relatedly, low-ABUK oxycodone became a significant factor in Purdue's ability in 2010 to bring Reformulated OxyContin® to market and subsequently maintain it there. In failing to consider this evidence, the court improperly discounted the nexus between regulatory compliance and commercial success. A48.

Finally, the court wholly ignored evidence showing Purdue and Rhodes's own **surprise** over their discovery and solution. A895. This evidence of unexpected and surprising results provides additional support for a finding of nonobviousness; the district court failed to consider it. *See Lindemann Maschinenfabrik GMBH v. Am. Hoist & Derrick Co.*, 730 F.2d 1452, 1461 (Fed. Cir. 1984) (clear error where "[t]he district court ignored the unexpected or surprising results achieved by the claimed invention").

In sum, these objective, real-world considerations are independent and compelling evidence of the claims' nonobviousness.

* * * *

The district court viewed its task as drawing "the line between patentable invention and commendable improvement." A71. Its analysis of obviousness, however, not only failed to recognize that "improvements" are themselves proper subjects for patenting (*see* 35 U.S.C. § 101), but also largely eviscerated the innovations, especially the discovery of 8α and its unique properties, that were the source of that "commendable improvement." The correct legal standards, applied to the court's own factual findings, establish that Purdue's commendable improvement was also patentable invention under Section 103. The judgment should be reversed as a matter of law.

II. THE CLAIMS OF THE '383 PATENT ARE VALID

In its brief, Grünenthal shows that Teva failed to prove by clear and convincing evidence that the '383 patent is invalid. As to anticipation, the McGinity application does not disclose three critical claim limitations of the '383 patent: (i) "opiates and opioids"; (ii) "with abuse potential"; or (iii) "a breaking strength" of any amount, much less "at least 500 N." A553 at 21:2-22:17. McGinity is directed to the different issue of controlled-release formulations, with no disclosure, expressly or inherently, of opiates or opioids, abuse potential, or breaking strength, much less in the manner claimed. *See* Grünenthal Br. 18-20, 26-40. Teva likewise failed to prove that the '383 claims were obvious. None of the prior art suggested the '383 patent's inventive formulation that deters abuse with a

super-hard tablet that still provides controlled release of an opioid drug. *See* Grünenthal Br. 18-22, 40-52.

Here, Purdue highlights evidence of nonobviousness that it presented based on its unique perspective as a '383 licensee. In particular, the success of Reformulated OxyContin® as a product in a regulated market is compelling evidence that the claims were not obvious. While commercial success as a proxy for nonobviousness often assumes a free market in which high sales would result from a patent's inventiveness, with respect to pharmaceuticals generally and Reformulated OxyContin® in particular, the market is restricted by its regulator, FDA, which will not permit drugs on the market that are not safe or effective.

FDA specifically recognized the value of the '383 inventions embodied in Reformulated OxyContin® and as a result prevented competition from generic copies of the original formulation. In April 2013, FDA made two extraordinary rulings. In finding that Reformulated OxyContin® was singularly entitled to abuse-deterrent labeling, FDA called out, *inter alia*, the hardness property: "The tablet is more difficult to crush, break, or dissolve." A85642-43. FDA also found, based on Reformulated OxyContin®'s abuse-deterrent properties in comparison with the safety risks presented by the original formulation lacking those properties, that Purdue withdrew its original formulation for reasons of safety. Because of that decision, FDA will not approve generic copies of the original formulation.

A85642-43. But for that regulatory decision, generic, less expensive versions of the original, non-abuse-deterrent formulation would have entered the market and sales of Reformulated OxyContin®, although a safer product, would have plummeted in the face of that market competition. A1211-23. Accordingly, each sale of Reformulated OxyContin® is directly related to the innovation of the '383 patent.

As with the low-ABUK patents, the district court clearly erred in evaluating obviousness without paying heed to FDA's control over and evaluation of regulated drugs. The court determined that there was no evidence of commercial success or nexus between the agency's views and the '383 patent because Reformulated OxyContin® did not generate more sales than the original formulation. A95-96. But because the original formulation is now deemed unsafe (due to its comparison with Reformulated OxyContin®), it makes no sense to compare sales of that unsafe product to those of the new one, particularly because a significant reason the old product was deemed unsafe is that it does not embody the '383 inventions. On those facts, there is plainly nexus between the "blockbuster" success of Reformulated OxyContin®—*i.e.*, its $2 billion annual sales—and the '383 patent. A1187-92; A1208-12; A88247. The court clearly erred in assessing the commercial success of Reformulated OxyContin® by reference to the market for original OxyContin®, rather than on the product's own

merits.

In *Leo Pharmaceuticals*, FDA approval supported a finding of commercial success where the approved product met a previously unmet medical need. *See* 726 F.3d at 1358. Reformulated OxyContin® was likewise designed to meet the need for an extended-release oral pain relief medication that could not be easily crushed. FDA's withdrawal of approval for original OxyContin® for reasons of safety demonstrated that there was a need for a safer, abuse-deterrent product—and that Reformulated OxyContin® met that need. This real-world evidence is compelling evidence of the nexus between the '383 patent and the commercial success of Reformulated OxyContin®.

The court's dismissal of FDA's approval of Purdue's abuse-deterrent labeling also missed the mark. A95-96. The court took the view that, since the labeling went into effect only a few months before trial, there was insufficient financial data to show whether the labeling change affected commercial success. A96. But regardless of the monetary valuation of the labeling, FDA's decision to permit Purdue to market Reformulated OxyContin® based on its abuse-deterrent qualities is itself evidence of commercial success. Given FDA's control over and evaluation of regulated drugs such as OxyContin®, its decision to approve abuse-deterrent labeling for Reformulated OxyContin®—the first time ever for an opioid drug—makes clear the nexus between sales of Reformulated OxyContin® and the

'383 technology it contains.

CONCLUSION

The judgments of invalidity of the '072, '799, '800, and '383 patents in Nos. 2014-1312 and -1314 (Purdue's claims against Teva) should be reversed, and the cases remanded for entry of judgment in favor of Purdue based on the district court's determinations of infringement. For the same reasons, the judgments of invalidity of the '072, '799, and '800 patents in Nos. 2014-1294, -1296, and -1306 (Purdue's claims against Epic, Mylan, and Amneal) should be reversed, and the cases remanded for further proceedings on Purdue's claims of infringement against those defendants.

Respectfully submitted,

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