United States Court of Appeals for the Federal Circuit

ALLERGAN, INC.,
Plaintiff-Appellee

v.

SANDOZ INC., LUPIN LTD., LUPIN PHARMACEUTICALS, INC., HI-TECH PHARMACAL CO., INC.,
Defendants-Appellants

2014-1275

Appeal from the United States District Court for the Eastern District of Texas in No. 6:11-cv-00441-MHS, Judge Michael H. Schneider.

Decided: August 4, 2015

JUANITA ROSE BROOKS, Fish & Richardson, P.C., San Diego, CA, argued for plaintiff-appellee. Also represented by CRAIG E. COUNTRYMAN; JONATHAN ELLIOT SINGER, DEANNA JEAN REICHEL, Minneapolis, MN; DOUGLAS E. MCCANN, SUSAN M. COLETTI, Wilmington, DE.

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CLARENCE DOYLE, ANDERS T. AANNESTAD, JAMES CEKOLA, San Diego, CA.

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STEVEN D. ROTH, Locke Lord, LLP, New York, NY, argued for defendant-appellant Hi-Tech Pharmacal Co., Inc. Also represented by THOMAS J. VETTER, Lucas & Mercanti, LLP, New York, NY.

Before LOURIE, LINN, and HUGHES, *Circuit Judges*.

LOURIE, *Circuit Judge*.

Sandoz Inc. ("Sandoz"), Lupin Ltd. and Lupin Pharmaceuticals, Inc. (collectively, "Lupin"), and Hi-Tech Pharmacal Co., Inc. ("Hi-Tech") (collectively, "the Appellants")[1] appeal from the decision of the United States District Court for the Eastern District of Texas, following a bench trial, which held that the claims of U.S. Patents 7,851,504 (the " '504 patent"), 8,278,353 (the " '353 patent"), 8,299,118 (the " '118 patent"), 8,309,605 (the " '605 patent"), and 8,338,479 (the " '479 patent"), asserted by Allergan, Inc. ("Allergan"), were not shown to be invalid for obviousness under 35 U.S.C. § 103, and that the

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[1] Watson Laboratories, Inc., Watson Pharmaceuticals, Inc., and Watson Pharm, Inc. (collectively, "Watson") were also defendants-appellants initially. But Watson has since been dismissed from this appeal on a joint motion filed by Watson and Allergan. *See Allergan, Inc. v. Sandoz Inc.*, No. 14-1275, ECF No. 121 (Fed. Cir. Apr. 17, 2015).

claims of the '353 and '118 patents were not shown to be invalid for lack of an adequate written description under 35 U.S.C. § 112, ¶ 1.[2] *Allergan, Inc. v. Sandoz Inc.*, No. 6:11-cv-00441, ECF No. 303, slip op. at 77, 79 (E.D. Tex. Jan. 13, 2014) ("*Opinion*"). Additionally, Lupin challenges the district court's determination that the claims of Allergan's patents were not shown to be invalid for lack of enablement under § 112, ¶ 1. *Id.* at 80–81. Hi-Tech also challenges the district court's finding that it infringed the claims of the '504, '605, and '479 patents literally and under the doctrine of equivalents. *Id.* at 64–66. For the reasons that follow, we *affirm* in all respects.

BACKGROUND

I

Glaucoma is an eye disease associated with elevated intraocular pressure ("IOP"). Treatments that effectively reduce IOP can slow the progression of the disease. If left untreated, however, elevated IOP can damage the optic nerve and lead to permanent vision loss and blindness. In 2001, the U.S. Food and Drug Administration (the "FDA") approved Lumigan® 0.03% ("Lumigan 0.03%"), a once-daily topical solution developed by Allergan, for treating open angle glaucoma and ocular hypertension. Lumigan 0.03% contains 0.03% by weight of bimatoprost and 50 parts per million ("ppm") benzalkonium chloride ("BAK"), among other ingredients.

Bimatoprost, the active ingredient in Lumigan 0.03%, is a prostaglandin analog that effectively lowers IOP, but can cause hyperemia, *i.e.*, red eye, when administered to

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[2] Because the applications resulting in the patents asserted in this case were filed before the enactment of the Leahy-Smith America Invents Act ("AIA"), Pub. L. No. 112-29, 125 Stat. 284 (2011), we apply the pre-AIA version of 35 U.S.C. § 103 and § 112.

the ocular surface. One structural difference between bimatoprost and two other prostaglandin analogs that were approved for treating glaucoma at the time of its approval, Xalatan® (latanoprost) and Travatan® (travoprost), is that bimatoprost contains an amide, instead of an ester as in latanoprost and travoprost. *Opinion* at 7–8. It was understood that both latanoprost and travoprost, but not bimatoprost, act as prodrugs of the corresponding acids. *Id.*

BAK is a preservative for inhibiting bacterial growth in ophthalmic solutions. It was known, however, that BAK is cytotoxic and that it can damage the cells on the ocular surface and cause undesirable side effects.

Although Lumigan 0.03% was effective at lowering IOP, it also caused frequent and severe hyperemia. Many patients thus stopped using it without consulting their physicians, which led to gradual vision loss. To address that problem, Allergan explored a number of alternative formulations of bimatoprost and surprisingly discovered that increasing the concentration of BAK from 50 ppm to 200 ppm significantly increased the corneal permeability of bimatoprost. *Id.* at 12–13. After further research, Allergan developed Lumigan® 0.01% ("Lumigan 0.01%").

Lumigan 0.01% is a topical solution containing 0.01% bimatoprost and 200 ppm BAK; otherwise, it has the same ingredients as Lumigan 0.03%. Thus, as compared with Lumigan 0.03%, Lumigan 0.01% has a three-fold lower bimatoprost concentration and a four-fold higher BAK concentration. Clinical studies showed that Lumigan 0.01% has similar efficacy to Lumigan 0.03%, *viz.*, IOP-lowering within 0.5 mmHg of that of Lumigan 0.03%, but it causes less frequent and severe hyperemia than Lumigan 0.03%. *Id.* at 20–21. In 2010, the FDA approved Allergan's New Drug Application for Lumigan 0.01% for the same approved uses as Lumigan 0.03%.

II

Allergan owns the '504, '353, '118, '605, and '479 patents, which are all listed in the FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (commonly known as the "Orange Book") as claiming Lumigan 0.01% and its approved uses. After Allergan received FDA-approval of Lumigan 0.01%, Sandoz, Lupin, Hi-Tech, and Watson each submitted an Abbreviated New Drug Application ("ANDA") to the FDA, seeking approval to engage in the commercial manufacture, use, importation, sale, or offer for sale of generic versions of Lumigan 0.01% prior to the expiration of the '504, '353, '118, '605, and '479 patents. In response, Allergan sued each of the ANDA applicants in the United States District Court for the Eastern District of Texas, asserting that their ANDA filings infringed those patents. The district court consolidated those actions into one case.

The asserted patents all derive from an application filed on March 16, 2005 and share a common specification. The patents are entitled "Enhanced Bimatoprost Ophthalmic Solution," '504 patent col. 1 ll. 1–2,[3] and refer to what is Lumigan 0.03% in the background section, *id.* col. 1 ll. 34–36. The specifications of the patents describe a composition comprising 0.005% to 0.02% bimatoprost and 100 ppm to 250 ppm BAK, which is an aqueous liquid "formulated for ophthalmic administration" and "useful in treating glaucoma or ocular hypertension." *Id.* col. 1 ll. 61–67. The specifications also specifically describe a formulation comprising *0.01%* bimatoprost and *200 ppm* BAK, among other formulations, as a "best mode" of the invention. *Id.* col. 2 ll. 59, 64–67.

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[3] Because the asserted patents share an identical specification in relevant part, we refer only to the '504 patent when discussing the specifications of those patents.

Additionally, the specifications disclose *in vitro* and *in vivo* experimental data in rabbits, showing that increasing the concentration of BAK from 50 ppm to 200 ppm significantly increased the permeability of bimatoprost across ocular membranes. *Id.* col. 4 ll. 10–58, col. 5 l. 19–col. 6 l. 5, Figs. 1 & 2. Finally, in a constructive example, the specifications describe the once-daily ophthalmic administration to a glaucoma patient of a formulation containing *0.015%* bimatoprost, *125 ppm* BAK, and 0.015% EDTA, stating that "intraocular pressure drops more and less hyperemia is observed than would be observed for [a formulation containing 0.03% bimatoprost and 50 ppm BAK,]" and "[l]owered intraocular pressure persists for as long as the treatment continues." *Id.* col. 6 ll. 7–14.

Allergan asserted the following claims against each of the ANDA applicants: claim 2 of the '504 patent; claim 15 of the '479 patent; claims 1, 6, 10, and 12 of the '605 patent; claims 1, 7, and 8 of the '353 patent; and claims 1, 7, and 8 of the '118 patent (collectively, "the asserted claims"). Those claims collectively are directed to compositions comprising bimatoprost and BAK and methods of using them to treat glaucoma or to lower IOP.

Each of the asserted claims requires a composition comprising 0.01% bimatoprost and 200 ppm BAK. Claim 2 of the '504 patent, claim 15 of the '479 patent, and claims 1, 6, 10, and 12 of the '605 patent (collectively, "the Group I claims") further require the composition to have a pH of "about 7.3." Claims 1, 7, and 8 of the '353 patent and claims 1, 7, and 8 of the '118 patent (collectively, "the Group II claims") do not contain such a pH limitation, but they require a particular clinical profile of the claimed composition as compared to a composition comprising 0.03% bimatoprost and 50 ppm BAK.

Claim 2 of the '504 patent is representative of the Group I composition claims and reads as follows:

> 2. A composition having *a pH of about 7.3* which comprises about *0.01% bimatoprost*, about *200 ppm benzalkonium chloride*, citric acid monohydrate, a phosphate buffer, and NaCl wherein said composition is an aqueous liquid which is formulated for ophthalmic administration.

Id. col. 6 ll. 21–25 (emphases added).

Claim 1 of the '605 patent is representative of the Group I method claims and reads as follows:

> 1. A method of lowering elevated intraocular pressure in a patient with open-angle glaucoma or ocular hypertension which comprises applying to the eyes of the patient an aqueous solution comprised of: about *0.01% w/v bimatoprost*; about *200 ppm benzalkonium chloride*; the solution having *a pH of about 7.3*; a phosphate buffer; and water.

'605 patent col. 5 ll. 47–55 (emphases added).

As indicated, the Group II claims all contain clinical profile limitations. Claims 1, 7, and 8 of the '353 patent are directed to compositions and read as follows:

> 1. A first composition administered once daily for lowering intraocular pressure in a person with glaucoma or ocular hypertension, the first composition comprising about 0.01% w/v bimatoprost and about 0.02% w/v benzalkonium chloride, wherein the first composition *lowers intraocular pressure and results in less hyperemia* as compared to the once daily administration of a second composition comprising 0.03% w/v bimatoprost and 0.005% w/v benzalkonium chloride.

> 7. A first composition administered once daily for lowering intraocular pressure in a person with glaucoma or ocular hypertension, the first compo-

> sition comprising about 0.01% w/v bimatoprost and about 0.02% w/v benzalkonium chloride, wherein the first composition *lowers intraocular pressure without a substantial reduction in the intraocular pressure lowering benefit* provided by the once daily administration of a second composition comprising 0.03% w/v bimatoprost and 0.005% w/v benzalkonium chloride.
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> 8. The composition of claim 7 wherein the once daily administration of the first composition results in *less hyperemia* as compared to the once daily administration of the second composition.

'353 patent col. 5 ll. 48–56, col. 6 ll. 3–15 (emphases added).[4] Claims 1, 7, and 8 of the '118 patent are directed to methods of treatment; they contain the same clinical profile limitations as those in claims 1, 7, and 8 of the '353 patent. '118 patent col. 5 ll. 48–56, col. 6 ll. 3–16.

III

The district court held a five-day bench trial in July 2013 on the issues of obviousness and infringement. The defendants also argued that the claims were invalid for lack of written description and enablement in pre- and post-trial briefings. In January 2014, the court rendered its findings of fact and conclusions of law on all of those issues.

a.

The district court concluded that the asserted claims would not have been obvious in view of the cited prior art, which included: (1) U.S. Patent 5,688,819 ("Woodward"); (2) U.S. Patent 6,933,289 ("Lyons"); (3) Laibovitz *et al.*, *Comparison of the Ocular Hypotensive Lipid AGN 192024*

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[4] The parties agree that 0.02% w/v corresponds to 200 ppm, and 0.005% w/v corresponds to 50 ppm.

with Timolol, 119 Archives of Ophthalmology 994 (2001) ("Laibovitz"); (4) Abelson *et al.*, *How to Handle BAK Talk*, Rev. of Ophthalmology, Dec. 2002, at 52–54 ("Abelson"); (5) Lee *et al.*, *Review: Topical Ocular Drug Delivery: Recent Developments and Future Challenges*, 2 J. Ocular Pharmacology 67 (1986) ("Lee"); (6) Camber *et al.*, *Factors Influencing the Corneal Permeability of Prostaglandin F_{2a} and Its Isopropyl Ester In Vitro*, 37 Int'l J. Pharmaceutics 27 (1987) ("Camber"); (7) Higaki *et al.*, *Estimation and Enhancement of In Vitro Corneal Transport of S-1033, a Novel Antiglaucoma Medication*, 132 Int'l J. Pharmaceutics 165 (1996) ("Higaki"); and (8) Keller *et al.*, *Increased Corneal Permeability Induced by the Dual Effects of Transient Tear Film Acidification and Exposure to Benzalkonium Chloride*, 30 Experimental Eye Res. 203 (1980) ("Keller").

Specifically, with respect to the scope and content of the prior art, the district court found that: (1) ophthalmic formulation was unpredictable, and it was not a field with a finite number of identified and predictable solutions, *Opinion* at 29–31; (2) Laibovitz and Lyons both taught that reducing bimatoprost from 0.03% to 0.01% would result in less IOP-lowering efficacy, *id.* at 31–34; (3) Laibovitz also taught that reducing bimatoprost from 0.03% to 0.01% would *not* result in less hyperemia, and Lyons did not suggest the contrary, *id.* at 34–35; (4) the cited prior art, including Higaki, Camber, Lee, Keller, and Abelson, as well as Xalatan® (latanoprost), which contains 200 ppm BAK, did *not* teach that high concentrations of BAK would enhance the corneal permeability of *bimatoprost*, a neutral prostaglandin amide analog; instead, the prior art suggested that BAK would *decrease* the permeability of a neutral prostaglandin analog, *id.* at 35, 38–47; and (5) the prior art taught that BAK should be minimized in ophthalmic formulations due to its toxicity, and, in particular, *taught away* from using 200 ppm BAK in a bimatoprost formulation because BAK was known to

cause side effects, including increased IOP, hyperemia, and dry eye, making it unsuitable for chronic use at high concentrations, *id.* at 47–54.

The district court then found that there would not have been a reason to pursue the claimed invention or a reasonable expectation of success if it were pursued. *Id.* at 55–56. The court also found evidence of long-felt need, unexpected results, and commercial success supporting a conclusion of nonobviousness. *Id.* at 56–59. The court specifically found that it was unexpected that Lumigan 0.01% would reduce the incidence and severity of hyperemia, as compared to Lumigan 0.03%, while maintaining IOP-lowering efficacy, and that it was also unexpected that 200 ppm BAK would enhance the permeability of bimatoprost to such an extent so as to allow the reduction of the bimatoprost concentration from 0.03% to 0.01% without loss of efficacy. *Id.* at 57–58.

In view of those factual findings, the district court concluded that the asserted claims would not have been obvious. *Id.* at 74. In reaching that conclusion, the court emphasized that the prior art taught away from the claimed invention because it taught "(1) that bimatoprost lost efficacy as its concentration decreased; (2) that BAK had no impact on bimatoprost's permeability; and (3) that BAK was cytotoxic and could cause corneal disorders, therefore encouraging the elimination or reduction in the concentration of BAK." *Id.* at 74–75.

The district court also rejected the defendants' argument raised in post-trial briefings that our decision in *Galderma Laboratories, L.P. v. Tolmar, Inc.*, 737 F.3d 731 (Fed. Cir. 2013), compels a conclusion of obviousness in this case. The defendants argued that Woodward disclosed a formulation comprising 0.001%–1% bimatoprost and 0–1000 ppm BAK for treating glaucoma, and that the amounts of bimatoprost and BAK in the claimed formulation fall within those prior art ranges, thus rendering the

claims obvious. The district court reasoned that "Allergan has met its burden of producing rebuttal evidence, i.e., 'that (1) the prior art taught away from the claimed invention; (2) there were new and unexpected results relative to the prior art; or (3) there are other pertinent secondary considerations.'" *Opinion* at 75 (quoting *Galderma*, 737 F.3d at 738). The court again emphasized that the prior art taught away from 200 ppm BAK, noting that the defendants' own expert, Dr. Samples, had serious concerns about BAK and strongly warned against its use. *Id.* at 75–76. The court also emphasized that the unexpected results were "of a different *kind*, not just of different *degree*." *Id.* at 76 (emphases in original).

The district court thus concluded that the defendants failed to prove by clear and convincing evidence that the asserted claims would have been obvious. *Id.* at 77.

b.

The district court also rejected the defendants' invalidity challenges based on the written description and enablement requirements, which they raised only in pre- and post-trial briefings. *Id.* at 77–81. The court noted that the defendants "did not present any evidence or argument" on those issues at trial. *Id.* at 77, 79.

Specifically, the defendants alleged that the Group II claims, which recite clinical profile limitations, were invalid for lack of an adequate written description. The district court found, however, that the patents explicitly describe the formulation of Lumigan 0.01%, and that Lumigan 0.01% has the clinical profile recited in the Group II claims. *Id.* at 78. The court also found additional support in the titles of the patents, the disclosed *in vitro* and *in vivo* permeability data of bimatoprost, as well as the constructive example comparing the IOP-lowering efficacy and hyperemia profile of a test formulation to that of Lumigan 0.03%. The court therefore found that the Group II claims have adequate written description

support, "especially given the express disclosure that Lumigan 0.01% is an example of the best mode of the invention." *Id.* The court additionally reasoned that the inventors had possession of the claimed invention because a clinical protocol prepared in November 2004, before the March 2005 application filing date, describes the formulation of Lumigan 0.01% and the later-claimed clinical profile. *Id.* at 79.

Lupin also alleged that the asserted claims were invalid for lack of enablement. The district court rejected that argument, reasoning that Allergan's patents disclose the formulation of Lumigan 0.01% and that the patents' disclosure would enable one of ordinary skill in the art to make and use the claimed invention without undue experimentation. *Id.* at 80–81.

c.

The district court also found that each of the ANDA products infringed each of the asserted claims. Relevant to this appeal, the court found that Hi-Tech's ANDA product infringed the Group I claims, which require the claimed composition to have a pH of "about 7.3." Before trial, the parties agreed to construe a "pH of about 7.3" as a "pH of approximately 7.3," and the court adopted that construction. *Allergan, Inc. v. Sandoz Inc.*, No. 6:11-cv-00441, 2013 WL 139350, at *9 (E.D. Tex. Jan. 10, 2013). Hi-Tech's ANDA specified that its proposed product has a pH of 6.8–7.2 during the product's shelf life. *Opinion* at 27. After considering the evidence presented at trial, the court found that Hi-Tech's ANDA product literally infringed the Group I claims. *Id.* at 64. The court also found, in the alternative, that Hi-Tech's ANDA product infringed the Group I claims under the doctrine of equivalents. *Id.* at 64–66.

Accordingly, the district court entered final judgment of infringement and no invalidity. The Appellants timely

appealed to this court; we have jurisdiction under 28 U.S.C. § 1295(a)(1).

DISCUSSION

Following a bench trial, we review a district court's conclusions of law *de novo* and its findings of fact for clear error. *Golden Blount, Inc. v. Robert H. Peterson Co.*, 365 F.3d 1054, 1058 (Fed. Cir. 2004). A factual finding is clearly erroneous if, despite some supporting evidence, we are left with a definite and firm conviction that a mistake has been made. *United States v. U.S. Gypsum Co.*, 333 U.S. 364, 395 (1948); *Alza Corp. v. Mylan Labs., Inc.*, 464 F.3d 1286, 1289 (Fed. Cir. 2006).

Furthermore, patents are presumed to be valid and overcoming that presumption requires clear and convincing evidence. 35 U.S.C. § 282; *Microsoft Corp. v. i4i Ltd. P'ship*, 564 U.S. __, 131 S. Ct. 2238, 2242 (2011).

I

We first consider the Appellants' arguments contending that the district court erred in concluding that the asserted claims would not have been obvious.

A patent claim is invalid as obvious if an alleged infringer proves that the differences between the claimed subject matter and the prior art are such that the subject matter as a whole would have been obvious at the time of invention to a person having ordinary skill in the art. 35 U.S.C. § 103(a) (2006). Obviousness is ultimately a question of law premised on underlying issues of fact, including: (1) the scope and content of the prior art; (2) the level of ordinary skill in the pertinent art; (3) the differences between the claimed invention and the prior art; and (4) objective evidence, such as commercial success, long-felt need, and the failure of others. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 427 (2007); *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966); *Monarch Knit-*

ting Mach. Corp. v. Sulzer Morat GmbH, 139 F.3d 877, 881 (Fed. Cir. 1998).

The Appellants argue that the district court erred as a matter of law by requiring them to establish a motivation to pursue the claimed formulation by modifying Lumigan 0.03% and a reasonable expectation of success in doing so. According to the Appellants, because the claimed amounts of bimatoprost and BAK fall within prior art ranges, the proper obviousness inquiry should focus only on teaching away, unexpected results, and other objective indicia. The Appellants also assert that the district court applied an incorrect standard for teaching away because it merely found that the prior art taught that the claimed formulation would be inferior, rather than that it would not work. And they argue that the prior art does not teach away from 0.01% bimatoprost or 200 ppm BAK. They assert, moreover, that there are no unexpected results because the observed results of similar efficacy and less hyperemia are only a difference in degree, not a difference in kind. They also argue that those results are the inherent properties of an otherwise obvious formulation. Finally, they argue that the district court erred in finding other objective indicia as supporting nonobviousness.

Allergan responds that this appeal turns on disputed facts and that the district court did not clearly err in finding those facts in Allergan's favor, including finding that the prior art taught that (1) 0.01% bimatoprost would be less efficacious than 0.03% bimatoprost; (2) BAK would decrease the permeability of bimatoprost; and (3) 200 ppm BAK would be unsafe for chronic use with bimatoprost. Allergan contends that the Appellants should not, on appeal, fault the district court for approaching the issue of obviousness in the way they argued it during trial. Allergan maintains that it would not have been obvious to modify Lumigan 0.03% to make the claimed formulation or to select the claimed amounts of bimatoprost and BAK from two very broad prior art

ranges. Allergan also responds that, in any event, the district court did not err in finding teaching away, unexpected results, and other objective indicia, which fully supported the court's conclusion of nonobviousness.

We agree with Allergan that the district court did not err in concluding that the asserted claims would not have been obvious. That conclusion is supported by underlying factual findings, which are not clearly erroneous on this record. In particular, the district court did not clearly err in finding that the prior art taught away from a formulation comprising 0.01% bimatoprost and 200 ppm BAK, and that such a formulation exhibited unexpected results.

It is undisputed that the asserted claims all require a formulation comprising 0.01% bimatoprost and 200 ppm BAK. Although the prior art does not teach that particular combination of amounts of bimatoprost and BAK, those amounts do fall within the ranges disclosed in a single reference: Woodward discloses a composition comprising 0.001%–1% bimatoprost and 0–1000 ppm of a preservative, including BAK. Those disclosed ranges also encompass Lumigan 0.03%, a prior art commercial embodiment, which contains 0.03% bimatoprost and 50 ppm BAK.

As we explained in *Galderma*, where there is a range disclosed in the prior art, and the claimed invention falls within that range, a relevant inquiry is whether there would have been a motivation to select the claimed composition from the prior art ranges. *Galderma*, 737 F.3d at 737–38 (prior art disclosing 0.01%–1% adapalene encompassing the claimed composition comprising 0.3% adapalene). In those circumstances, "the burden of production falls upon the patentee to come forward with evidence that (1) the prior art taught away from the claimed invention; (2) there were new and unexpected results relative to the prior art; or (3) there are other pertinent secondary considerations." *Id.* at 738.

Here in this case, the prior art ranges are broader than the range in *Galderma*, and the record shows that the claimed amounts of the two different ingredients could and did materially and unpredictably alter the property of the claimed formulation. Thus, *Galderma* does not compel a conclusion of obviousness in this case. It may also be true here that "the disclosed range[s are] so broad as to encompass a very large number of possible distinct compositions," *In re Peterson*, 315 F.3d 1325, 1330 n.1 (Fed. Cir. 2003), such that they do not teach any specific amounts or combinations and that the burden of producing evidence of teaching away, unexpected results, and other pertinent secondary considerations did not shift to Allergan. But we need not decide that issue, as it would not affect our affirmance of the district court's conclusion of nonobviousness, because, as indicated *infra*, we conclude that the district court did not clearly err in finding that Allergan had produced ample evidence of teaching away and unexpected results, and that such evidence fully supports a conclusion of nonobviousness.

"Whether the prior art teaches away from the claimed invention is a question of fact." *Spectralytics, Inc. v. Cordis Corp.*, 649 F.3d 1336, 1343 (Fed. Cir. 2011). "A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994).

The district court did not clearly err in finding that the prior art taught away from using 200 ppm BAK in a bimatoprost formulation. As the district court found, the prior art taught that BAK should be minimized in ophthalmic formulations to avoid safety problems. *Opinion* at 49. Indeed, the Appellants' own expert summarized the prior art's widespread concern by describing BAK as "a natural-born killer" that was "from Satan." *Id.* at 75–

76. Specifically, as the district court found in great detail, BAK was known to cause increased IOP, hyperemia, dry eye, and damage to corneal cells, and to exacerbate other eye disorders. *Id.* at 40–54. It is not clearly erroneous to find that those known side effects would have discouraged a person of ordinary skill from using higher concentrations of BAK in a bimatoprost formulation, especially when 50 ppm BAK was known to be an adequate preservative in Lumigan 0.03%.

While it is true that the prior art, such as Abelson, also disclosed ophthalmic formulations containing 200 ppm BAK, the district court correctly found that those formulations, with the exception of Xalatan® and Xalacom, were "not for chronic long-term use" and "would teach nothing about whether it was safe to use 200 ppm BAK with a *lifelong* glaucoma drug." *Id.* at 53 (emphasis added). With respect to Xalatan® and Xalacom, both of which contain 200 ppm BAK and latanoprost, a prostaglandin ester analog, the district court found that "the majority of BAK in solution complexed with latanoprost and was not free in solution to interact with the epithelial cells," *id.* at 40, 53–54; and, moreover, that Xalatan® "showed a decrease in cell membrane integrity and a significant increase in apoptosis" as compared to a formulation with less BAK, which would have discouraged the skilled artisan from increasing the amount of BAK in a bimatoprost formulation, *id.* at 52. Those factual findings are not clearly erroneous.

Moreover, the district court did not clearly err in finding that the prior art taught that BAK would *not* increase the permeability of bimatoprost, but might instead decrease it. *Id.* at 35, 38–47. The district court found that Higaki and Camber taught that BAK reduced the permeability of *uncharged* prostaglandin analogs that are similar to bimatoprost, *id.* at 38–40, and that the other cited references, including Lee, Keller, and Abelson, did not teach that BAK would enhance the permeability of

bimatoprost because those references studied large, charged, or hydrophilic molecules that are dissimilar to bimatoprost, *id.* at 41–47. In view of those factual findings, there would not have been a reason to use 200 ppm BAK in a bimatoprost formulation. *See DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) ("An inference of nonobviousness is especially strong where the prior art's teachings undermine the very reason being proffered as to why a person of ordinary skill would have combined the known elements.").

The record thus shows that the prior art "criticize[d], discredit[ed], or otherwise discourage[d]" the use of 200 ppm BAK in a bimatoprost formulation. *In re Mouttet*, 686 F.3d 1322, 1334 (Fed. Cir. 2012) (quoting *In re Fulton*, 391 F.3d 1195, 1201 (Fed. Cir. 2004)). We therefore need not address the Appellants' additional argument that the district court erred in finding that Laibovitz and Lyons taught away from 0.01% bimatoprost. The Appellants do not argue, and there is no evidence to suggest, that Laibovitz and Lyons favored using 200 ppm BAK in a bimatoprost formulation. Accordingly, we conclude that the district court did not clearly err in finding that the prior art taught away from the claimed formulation.

We also conclude that the district court did not clearly err in finding that the claimed formulation exhibited "unexpected results," which differed in kind, not just in degree, from the prior art. *Opinion* at 57–58, 76. As indicated, the prior art taught that 200 ppm BAK would either have no impact on the permeability of bimatoprost or decrease it. Allergan's inventors surprisingly determined that the opposite was true, namely, that 200 ppm BAK enhanced the permeability of bimatoprost. That is an unexpected difference in kind that supports nonobviousness. *In re Applied Materials, Inc.*, 692 F.3d 1289, 1298 (Fed. Cir. 2012) ("Evidence that the variables inter-

acted in an unpredictable or unexpected way could render the combination nonobvious.") (citing *KSR*, 550 U.S. at 421).

Moreover, the district court properly found that Laibovitz taught that reducing bimatoprost from 0.03% to 0.01% resulted in significantly reduced efficacy, *Opinion* at 31–33, but that such a reduction in bimatoprost did not result in less hyperemia, *id.* at 34. The claimed formulation, which comprises 0.01% bimatoprost and 200 ppm BAK, unexpectedly maintained the IOP-lowering efficacy of Lumigan 0.03%, while exhibiting reduced incidence and severity of hyperemia, even though the prior art taught that BAK could cause hyperemia at high concentrations. Those results exhibited by the claimed formulation thus constitute an unexpected difference in kind, *viz.*, the difference between an effective and safe drug and one with significant side effects that caused many patients to discontinue treatment.

Finally, we reject the Appellants' argument that the unexpected results do not support nonobviousness because they are merely the inherent properties of an otherwise obvious formulation. As indicated, the prior art did not disclose, either explicitly or implicitly, the claimed formulation; rather, it taught away from such a formulation. A person of ordinary skill in the art thus would not have had a reason to select the claimed formulation from the prior art ranges or to modify Lumigan 0.03% to arrive at the claimed formulation. The unexpected properties of the claimed formulation, even if inherent in that formulation, differ in kind from the prior art, thereby supporting a conclusion of nonobviousness. *See W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1555 (Fed. Cir. 1983) ("Inherency and obviousness are distinct concepts."); *In re Spormann*, 363 F.2d 444, 448 (CCPA 1966) ("That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown.").

This is not a case where the claims merely recite the unknown properties of an otherwise obvious formulation. *E.g.*, *Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1354 (Fed. Cir. 2012) ("[A]n obvious formulation cannot become nonobvious simply by administering it to a patient and claiming the resulting serum concentrations."); *In re Kao*, 639 F.3d 1057, 1070 (Fed. Cir. 2011) ("Maloney's express teachings render the claimed controlled release oxymorphone formulation obvious, and the claimed 'food effect' adds nothing of patentable consequence."). Here, the previously *unknown* and *unexpected* properties of a new and nonobvious formulation constitute additional, objective evidence of nonobviousness.

We have considered the remaining arguments on the issue of obviousness but find them unpersuasive. For the foregoing reasons, we affirm the district court's holding that the asserted claims would not have been obvious in view of the cited references.

II

We next consider the Appellants' arguments contending that the district court erred in finding that the Group II claims are not invalid for lack of an adequate written description, and Lupin's arguments contending that the court erred in holding that the asserted claims are not invalid for lack of enablement.

Section 112 of the patent statute provides in relevant part that:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same . . . .

35 U.S.C. § 112, ¶ 1 (2006). "[T]his statutory language mandates satisfaction of two separate and independent requirements: an applicant must both describe the claimed invention adequately and enable its production and use." *Alcon Research Ltd. v. Barr Labs., Inc.*, 745 F.3d 1180, 1188 (Fed. Cir. 2014) (citing *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1344 (Fed. Cir. 2010) (en banc); *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1562–63 (Fed. Cir. 1991)).

a.

"Whether a claim satisfies the written description requirement is a question of fact that, on appeal from a bench trial, we review for clear error." *Alcon*, 745 F.3d at 1190. The written description requirement is met when the disclosure "allow[s] one skilled in the art to visualize or recognize the identity of the subject matter purportedly described." *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 323 F.3d 956, 968 (Fed. Cir. 2002). There is no rigid requirement that the disclosure contain "either examples or an actual reduction to practice"; the proper inquiry is whether the patentee has provided an adequate description that "in a definite way identifies the claimed invention" in sufficient detail such that a person of ordinary skill would understand that the inventor had made the invention at the time of filing. *Ariad*, 598 F.3d at 1352. That assessment "requires an objective inquiry into the four corners of the specification," as "the hallmark of written description is disclosure." *Id.* at 1351.

The Appellants argue that the claims of the '353 and '118 patents (the Group II claims), which recite clinical profile limitations, are not adequately supported by the written description because the written description does not disclose any efficacy or hyperemia data of a formulation comprising 0.01% bimatoprost and 200 ppm BAK. The Appellants assert that the district court erred by relying on the permeability data of test formulations

(which are not efficacy or hyperemia data), the constructive example (which relates to a formulation comprising 0.015% bimatoprost and 125 ppm BAK), and the clinical protocol (which is not part of the specifications). Hi-Tech additionally argues that there are no "blaze marks" in the specifications to allow the skilled artisan to immediately discern the clinical profile claim limitations.

Allergan responds that the district court did not clearly err in finding that the Appellants failed to prove lack of an adequate written description by clear and convincing evidence. Allergan argues that the written description here adequately describes the claimed invention because it identifies the exact formulation of Lumigan 0.01% as a best mode of the invention and Lumigan 0.01% exhibited the claimed clinical results. Allergan also responds that the district court referenced the clinical protocol simply to corroborate what the specifications show. Allergan also maintains that the disclosed permeability data and the constructive example are relevant to the written description inquiry as they would allow the skilled artisan to predict the clinical performance of Lumigan 0.01%.

We agree with Allergan that the specifications of the asserted patents provide an adequate written description of the invention claimed by the Group II claims. The specifications specifically describe a formulation comprising 0.01% bimatoprost and 200 ppm BAK as one of the best modes of the invention. '504 patent col. 2 ll. 59, 64–67. The Group II claims all require the same amounts of bimatoprost and BAK. The specifications thus disclose the claimed formulation as characterized by those ingredients, and the skilled artisan would immediately discern the claimed formulation in that disclosure.

It is true that the Group II claims also recite clinical profile limitations and the specifications do not explicitly describe the clinical efficacy and hyperemia profile of the claimed formulation. But the Appellants have empha-

sized, in connection with their obviousness challenge, that the inherent properties of a formulation comprising 0.01% bimatoprost and 200 ppm BAK produce the claimed clinical profile. Sandoz's Opening Br. 51 (stating that "the claimed clinical effects *necessarily* result from using 0.01% bimatoprost and 200 ppm BAK" (emphasis in original) (citing J.A. 5537–41, 5764–66)); Lupin's Opening Br. 23 (incorporating Sandoz's opening brief by reference); Hi-Tech's Opening Br. 24 (same). A claim that recites a property that is necessarily inherent in a formulation that is adequately described is not invalid as lacking written description merely because the property itself is not explicitly described. On this particular record, we agree with the district court that the Appellants have failed to prove invalidity for lack of an adequate written description by clear and convincing evidence. *See Enzo Biochem*, 323 F.3d at 963 ("Compliance with the written description requirement is essentially a fact-based inquiry that will necessarily vary depending on the nature of the invention claimed." (internal quotation marks omitted)).

We do find, however, that the district court erred by relying on the undisclosed clinical protocol to support its written description determination. As we have explained, "[i]t is the disclosures of the applications that count." *Lockwood v. Am. Airlines, Inc.*, 107 F.3d 1565, 1571 (Fed. Cir. 1997). The clinical protocol is not part of the specifications of the asserted patents. It should not form the basis of the written description inquiry, even if it shows that the inventors had invented the claimed invention before the time of filing. The written description requirement requires possession *as shown in the specification*, not as shown by prior experimental work. Nevertheless, as indicated, because the specifications contain an adequate disclosure of the claimed formulation, the district court's erroneous reliance on the clinical protocol does not affect the outcome of this case.

We have considered the remaining arguments on the issue of written description but find them unpersuasive. We therefore conclude that the district court did not err in finding that the Appellants failed to prove by clear and convincing evidence that the Group II claims are invalid for lack of an adequate written description.

b.

Whether a claim satisfies the enablement requirement is a question of law that we review without deference. *Alcon*, 745 F.3d at 1188. We review the factual issues underlying enablement for clear error. *Id.* To prove that a claim is invalid for lack of enablement, a challenger must show by clear and convincing evidence that a person of ordinary skill in the art would not be able to practice the claimed invention without "undue experimentation." *Id.* (quoting *In re Wands*, 858 F.2d 731, 736–37 (Fed. Cir. 1988)).

Lupin argues that the asserted claims are invalid for lack of enablement because the specifications contain no actual efficacy and hyperemia data; rather, they merely provide a research proposal. According to Lupin, the skilled artisan would not accept without doubt the asserted utility of the claimed formulation, *i.e.*, comparable efficacy as Lumigan 0.03% and less hyperemia. Lupin argues that if the claims are held to be nonobvious, then they must fail the enablement requirement because the district court found that ophthalmic formulation is unpredictable and that the prior art taught away from the claimed invention.

Allergan responds that there is no inconsistency in the district court's decision that the asserted claims would not have been obvious and that they are also enabled. Allergan argues that the specifications disclose the exact formulation of Lumigan 0.01% and the permeability data of test formulations, which would enable the skilled artisan to make and use the claimed invention. Allergan

also responds that, in view of the patents' disclosure, the skilled artisan would not have questioned the utility of the claimed formulation.

We agree with Allergan that the asserted claims are not invalid for lack of enablement. "[A] patent does not need to guarantee that the invention works for a claim to be enabled." *Alcon*, 745 F.3d at 1189. And efficacy data are generally not required in a patent application. Only a sufficient description enabling a person of ordinary skill in the art to carry out an invention is needed. "Similarly, a patentee is not required to provide actual working examples; we have rejected enablement challenges based on the theory that there can be no guarantee that prophetic examples actually work." *Id.* at 1189–90.

Here, the asserted claims require a formulation comprising specific amounts of bimatoprost and BAK. The patents refer to what is Lumigan 0.03%, which was a known drug for treating glaucoma. '504 patent col. 1 ll. 34–36. The specifications disclose actual *in vitro* and *in vivo* data, showing that increasing the amount of BAK unexpectedly increased the permeability of bimatoprost across ocular membranes. *Id.* col. 4 ll. 10–58, col. 5 l. 19–col. 6 l. 5, Figs. 1 & 2. In a constructive example, the specifications teach that a formulation containing 0.015% bimatoprost and 125 ppm BAK would effectively reduce IOP and also exhibit less hyperemia than Lumigan 0.03%. *Id.* col. 6 ll. 7–14. In view of those disclosures, we agree with the district court that the skilled artisan would not have questioned the utility of the claimed formulation and would be able to make and use the claimed invention without undue experimentation.

Lupin argues that "if the asserted claims are non-obvious, they cannot possibly be enabled." Lupin's Opening Br. 28. We disagree. The obviousness inquiry turns on what the prior art would have taught a person of ordinary skill in the art and whether the claimed inven-

tion would have been obvious in view of the *prior art*. As indicated, the claims here would not have been obvious because, among other reasons, the prior art taught that BAK would not increase the permeability of bimatoprost. In contrast, the enablement inquiry turns on whether the skilled artisan, after reading the *specification*, would be able to make and use the claimed invention without undue experimentation, based on the ordinary skill in the art. Because the specifications here provide sufficient guidance to the skilled artisan, there is no tension in the district court's decision that the asserted claims would not have been obvious and also are not invalid for lack of enablement.

We have considered the remaining arguments on the issue of enablement but find them unpersuasive. We therefore affirm the district court's holding that Lupin failed to prove by clear and convincing evidence that the asserted claims are invalid for lack of enablement.

III

Finally, we address Hi-Tech's arguments contending that the district court erred in finding that its ANDA product infringed, both literally and under the doctrine of equivalents, the Group I claims, which require the claimed composition to have a "pH of about 7.3." A determination of infringement, whether literal or under the doctrine of equivalents, is a question of fact and is reviewed for clear error following a bench trial. *Biovail Corp. Int'l v. Andrx Pharm., Inc.*, 239 F.3d 1297, 1300 (Fed. Cir. 2001). "Prosecution history estoppel operates as a legal limitation on a patentee's ability to invoke the doctrine of equivalents, and we review its application *de novo*." *Trading Techs. Int'l, Inc. v. Open E Cry, LLC*, 728 F.3d 1309, 1318 (Fed. Cir. 2013).

Hi-Tech argues that the district court erred in construing a "pH of about 7.3." Hi-Tech also argues that the district court erred in finding that Hi-Tech literally in-

fringed the Group I claims and that prosecution history estoppel did not bar Allergan from relying on the doctrine of equivalents to prove infringement. Allergan responds that Hi-Tech stipulated to the claim construction in the district court and cannot now allege error for the first time on appeal. Allergan also responds that the district court did not clearly err in finding both literal infringement and infringement under the doctrine of equivalents.

We agree with Allergan that the district court did not clearly err in finding that Hi-Tech literally infringed the Group I claims. In the district court, the parties agreed to construe a "pH of about 7.3" as a "pH of approximately 7.3," and the district court adopted that construction. Hi-Tech did not argue for further construction in the district court. That construction thus controls in this case.

It is undisputed that Hi-Tech's ANDA specifies that its proposed product has a pH of 6.8–7.2 during the product's shelf life. The district court thus correctly evaluated infringement based on the proposed product. *Sunovion Pharm., Inc. v. Teva Pharm. USA, Inc.*, 731 F.3d 1271, 1278–80 (Fed. Cir. 2013). After considering the expert testimony proffered by both sides, the district court found that Hi-Tech's product would infringe the Group I claims literally. We find no clear err in that determination. Moreover, if "about 7.3" is to mean anything other than 7.3, it is not clearly erroneous for it to include a value that differs from it by only one decimal place. Because we affirm the district court's finding of literal infringement, we do not need to address whether the district court erred in finding infringement under the doctrine of equivalents.

We have considered Hi-Tech's remaining arguments but find them unpersuasive. For the foregoing reasons, we affirm the district court's finding that Hi-Tech infringed the Group I claims.

CONCLUSION

Accordingly, we affirm the district court's determination that the asserted claims are not invalid for obviousness or for lack of an adequate written description and enablement, and that Hi-Tech infringed the claims of the '504, '605, and '479 patents.

AFFIRMED