United States Court of Appeals for the Federal Circuit

SENJU PHARMACEUTICAL CO., LTD., KYORIN PHARMACEUTICAL CO., LTD., ALLERGAN, INC.,
Plaintiffs-Appellants

v.

LUPIN LIMITED, LUPIN PHARMACEUTICALS, INC.,
Defendants-Appellees

HI-TECH PHARMACAL CO., INC.,
Defendant-Appellee

2013-1630

Appeal from the United States District Court for the District of Delaware in No. 11-CV-0271, 11-CV-0439, 11-CV-0926, 11-CV-1059, Judge Sue L. Robinson.

Decided: March 20, 2015

MARK ANDREW PERRY, Gibson, Dunn & Crutcher LLP, Washington, DC, argued for plaintiffs-appellants. Also represented by JEFFREY T. THOMAS, Irvine, CA, LUCAS C. TOWNSEND, Washington, DC; RICHARD D. KELLY, FRANK JONAH WEST, STEPHEN G. BAXTER, Oblon, Spivak, McClelland, Maier & Neustadt, LLP, Alexandria, VA.

DEANNE M. MAZZOCHI, Rakoczy Molino Mazzochi Siwik LLP, Chicago, IL, argued for defendants-appellees Lupin Limited, Lupin Pharmaceuticals, Inc. Also represented by WILLIAM A. RAKOCZY, PAUL J. MOLINO, ANUJ KUMAR WADHWA, JOHN POLIVICK, BRIAN PETER MURRAY.

JEFFREY T. CASTELLANO, Shaw Keller LLP, Wilmington, DE, argued for defendant-appellee Hi-Tech Pharmacal Co., Inc. Also represented by KAREN E. KELLER; STEVEN D. ROTH, Locke Lord, LLP, New York, NY.

Before NEWMAN, PLAGER, and MOORE, *Circuit Judges.*

Opinion for the court filed by *Circuit Judge* PLAGER.

Dissenting opinion filed by *Circuit Judge* NEWMAN.

PLAGER, *Circuit Judge.*

This is a patent case brought under the Hatch-Waxman Act, Pub. L. No. 98-417, 98 Stat. 1585 ("the Act"), on appeal from the United States District Court for the District of Delaware. Pursuant to the Act, plaintiffs-appellants Senju Pharmaceutical Co., Ltd., Kyorin Pharmaceutical Co., Ltd., and Allergan, Inc. (collectively "Senju") sued defendants-appellees Lupin Limited and Lupin Pharmaceuticals, Inc. (collectively "Lupin") and Hi-Tech Pharmacal Co., Inc. ("Hi-Tech") for infringement of asserted claims 6 and 12-16 of reexamined U.S. Patent No. 6,333,045 ("the '045 patent"). Defendants counterclaimed seeking a declaratory judgment of non-infringement and invalidity. The district court, Judge Sue L. Robinson, adjudged the claims infringed but inva-

lid for obviousness. Plaintiffs appeal the invalidity judgment.[1]

I. INTRODUCTION

The invention at issue relates to gatifloxacin, an aqueous liquid pharmaceutical eye drop composition, with added disodium edetate ("EDTA"). Seven prior art patents are alleged as the basis for the obviousness determination, each containing some of the same chemistry as the claimed invention. In addition, there are several prior patent infringement suits involving the same chemistry and the same '045 patent; these suits are relevant, though to some extent the issues and parties vary. Three of these infringement suits, including this one, have all been tried before and decided by the same district judge in the District of Delaware.

The underlying issues in this case—constructive infringement under Hatch-Waxman, countered by alleged non-infringement and invalidity for obviousness—are familiar patent issues. Yet, the combination of the chemistry and the prior litigation has produced here a complex of arguments by both parties. We address below in detail only those arguments that we believe have saliency with regard to the outcome.

Regarding the prior law suits, the first began in 2007. Pursuant to the Hatch-Waxman Act, a manufacturer of generic drugs, Apotex Inc. and Apotex Corp. ("Apotex"), filed an Abbreviated New Drug Application ("ANDA") with the Food and Drug Administration ("FDA"), seeking to market generic versions of Allergan's

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[1] Hi-Tech filed a brief in which it adopted by reference and joined most of Lupin's brief. Hi-Tech's additional arguments in its brief relate to issues of intervening rights, which in view of the outcome we need not address in this opinion.

gatifloxacin product Zymar®. The patent on Zymar® was listed in the FDA's record of Approved Drug Products With Therapeutic Equivalence, what is known as the "Orange Book."

In this first suit, the district court in 2010 ruled that the asserted claims were infringed, but that claims 1-3 and 6-9 were invalid as obvious over the prior art. However, the court found that defendant Apotex failed to demonstrate that claims 6 and 7 were invalid for lack of enablement and failed to demonstrate inequitable conduct. *Senju Pharm. Co. v. Apotex Inc.*, 717 F. Supp. 2d 404, 433 (D. Del. 2010) ("*Apotex 1*").

Following a motion for a new trial, or, alternatively, to amend judgment and findings regarding claim 7, the court reopened the case to consider additional evidence regarding claim 7. Thereafter, the court in 2011 found claim 7 obvious by clear and convincing evidence. *Senju Pharm. Co. v. Apotex Inc.*, 836 F. Supp. 2d 196, 210-11 (D. Del. 2011) ("*Apotex 2*"). On appeal of the judgment regarding claim 7, this court affirmed the judgment of invalidity in a summary affirmance, *Senju Pharm. Co. v. Apotex Inc.*, 485 F. App'x 433 (Fed. Cir. 2012) ("*Apotex I*"); the other parts of the district judge's rulings were not appealed.

Meanwhile, in February 2011, before final judgment was entered in that litigation, the Senju plaintiffs petitioned the Patent and Trademark Office ("PTO") for ex-parte re-examination of the '045 patent. Plaintiffs submitted the prior art, the arguments relied upon by the court and parties, and the court's opinion. However, plaintiffs did not notify either the defendants or the court that they were seeking re-examination; it was not until shortly before the re-examination was completed that the trial court was informed.

On initial reexamination, the PTO agreed with the district court that the original claims would have been

obvious in light of the cited prior art patents. Subsequently, in October 2011, the PTO issued a reexamination certificate for the '045 patent which cancelled claims 1-3 and 8-11, allowed amended claim 6, and added claims 12-16.

Then plaintiff Senju filed another suit against Apotex, alleging infringement of the reexamined claims and seeking a declaratory judgment of infringement based on the same ANDA filing at issue in the first litigation. Apotex responded to the new action by seeking dismissal on the grounds of res judicata, or claim preclusion ("claim" here referring to the civil procedure concept, not the patent law meaning).

Ultimately the district court sided with Apotex and gave judgment against Senju on the grounds of claim preclusion: "the reexamination of the patent-at-issue did not create a new cause of action against the same previous defendants and accused product." *Senju Pharm. Co. v. Apotex Inc.*, 891 F. Supp. 2d 656, 662 (D. Del. 2012) ("*Apotex 3*"). On appeal, this judgment was upheld in an extensive opinion by the Federal Circuit, *Senju Pharm. Co. v. Apotex Inc.*, 746 F.3d 1344 (Fed. Cir. 2014) ("*Apotex II*").

While all this was going on, Senju, in 2011, filed the suit at issue here against the Lupin and Hi-Tech defendants, asserting infringement under the Hatch-Waxman Act of the '045 patent.[2] As in the second suit against Apotex, Senju specifically alleged infringement of the reexamined claims 6 and 12-16, this time based on Lu-

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[2] Civ. No. 11-271, filed March 31, 2011, against Lupin, was consolidated with Civ. Nos. 11-439, filed May 18, 2011, against Lupin, as well as 11-926, filed October 11, 2011, and 11-1059, filed October 31, 2011, against Hi-Tech.

pin's earlier-filed ANDA Nos. 202-653, 0.5 w/v% gatifloxacin and 202-709, 0.3 w/v% gatifloxacin, as well as Hi-Tech's ANDA Nos. 203189, 0.5 w/v% gatifloxacin and 203190, 0.3 w/v% gatifloxacin. The Lupin and Hi-Tech defendants had sought FDA approval to market and sell generic copies of Senju's FDA approved gatifloxacin ophthalmic solution.

Lupin moved for judgment on the pleadings, alleging that the narrower reexamined claims of the '045 patent were invalid for obviousness, and that plaintiffs should be collaterally estopped from relitigating these claims based on the court's findings in *Apotex 3*. The district court ruled that, although Lupin might later at trial succeed in showing that the reexamined claims were invalid for obviousness, Senju in the *Apotex 1 & 2* litigations had not fully litigated a claim with a limitation of 0.01 w/v% EDTA and, therefore, collateral estoppel would not apply.[3] J.A. 7.

As noted earlier, the '045 patent is directed to aqueous liquid pharmaceutical compositions comprising gatifloxacin and EDTA, as well as various methods utilizing these compositions. The '045 patent's original U.S. filing date is April 21, 2000. The reexamined claims at issue are:

> 6. A method for raising corneal permeability of an aqueous pharmaceutical Gatifloxacin eye drop solution comprising Gatifloxacin or its salt, having a pH of from above 5 to about 6 containing from about 0.3 to about 0.8 w/v% Gatifloxacin or its salt, which comprises incorporating about 0.01

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[3] At the time of trial, the district court declined to entertain Lupin's renewed collateral estoppel argument. J.A. 7.

> w/v% disodium edetate into said Gatifloxacin eye drop solution.
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> 12. An aqueous liquid pharmaceutical eye drop composition which comprises from about 0.3 to about 0.8 w/v% Gatifloxacin or its salt, about 0.01 w/v% disodium edetate, and wherein the aqueous liquid pharmaceutical composition has a pH of from about 5 to about 6.
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> 13. The aqueous liquid pharmaceutical eye drop composition according to claim 12, comprising about 0.3 w/v% Gatifloxacin or its salt.
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> 14. The aqueous liquid pharmaceutical eye drop composition according to claim 12, comprising about 0.5 w/v% Gatifloxacin or its salt.
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> 15. The aqueous liquid pharmaceutical eye drop composition according to claim 12, comprising at least one isotonic agent selected from the group consisting of sodium chloride, potassium chloride, glycerin, mannitol and glucose.
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> 16. The aqueous liquid pharmaceutical eye drop composition according to claim 14, wherein the at least one isotonic agent is sodium chloride.

'045 patent Reexamination Certificate, 1:25-2:24; J.A. 2702.

The district court, having reserved the question of infringement and the validity of the reexamined claims in light of the prior art of record, proceeded to trial. The court's ultimate judgment was that the reexamined claims were infringed, but were invalid for obviousness. Thus, the question before us is in this appeal is whether the district court erred when, in the current suit against Lupin and Hi-Tech, it concluded that reexamined claims 6 and 12-16 of the '045 patent were invalid for obviousness.

We have jurisdiction under 28 U.S.C. §§ 1292(c)(2) and 1295(a).

II. DISCUSSION

A. Standard of Review

Obviousness is a question of law that we review without deference. *Pozen Inc. v. Par Pharm., Inc.*, 696 F.3d 1151, 1160 (Fed. Cir. 2012). Following a bench trial, we review underlying factual determinations for clear error. *Id.*

An obviousness inquiry assesses "the differences between the subject matter sought to be patented and the prior art" to ascertain whether "the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103(a) (1994). "[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007). Thus, a defendant asserting obviousness in view of a combination of references has the burden to show by clear and convincing evidence that a person of ordinary skill in the relevant field had reason to combine the elements in the manner claimed. *Id.* at 418-19. In addition to showing a reason to combine the elements in the manner claimed, a defendant must also demonstrate that a person of ordinary skill would have a reasonable expectation of success in combining the elements. *PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342, 1360 (Fed. Cir. 2007).

B. Analysis

The Senju appellants make two main arguments relating to obviousness: (1) the district court erred by finding that the prior art taught using 0.01 w/v% EDTA in an ophthalmic formulation would work to increase corneal

permeability; and (2) the district court erred by finding appellants' proffer of evidence of unexpected results unavailing. We will consider each of these arguments in turn.

1. Obviousness

Before addressing the substantive obviousness analysis conducted by the district court, we address Senju's arguments regarding the methodology the district court used in its analysis. First, appellants argue that the district court improperly utilized its obviousness findings from its decision in *Apotex 1* as the basis from which to begin its invalidity inquiries in this case, essentially lessening appellees' burden of proving by clear and convincing evidence that the reexamined claims asserted in the present case would have been obvious. Appellants argue that the district court's factual findings in *Apotex 1* should have played no role in the invalidity inquiry in this case because the currently asserted reexamined claims contain new limitations and disclose only a narrow subset of the original claimed invention, commensurate with objective evidence of unexpected results.

Appellants argue that the district court relied upon findings from *Apotex 1* regarding EDTA concentrations and pH range to conclude that the new limitations in the reexamined claims do not distinguish the claimed inventions from the prior art. They argue that the court analyzed the claims in piecemeal fashion, violating the requirement in section 103 of the Patent Act that courts analyze the obviousness of an invention "as a whole." *See* 35 U.S.C. § 103(a).

Appellants argue that the district court by this method of analysis effectively applied a presumption of invalidity to the reexamined claims, resulting in the district court's failure to evaluate the limitations holistically. In effect, appellants argue, the district court used the predecessor claims as prior art to the present claims even

though such methodology is erroneous as a matter of law. Appellant Br. 63-64 (citing *Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1137 (Fed. Cir. 1985)).

Appellees respond that appellants' pursuit of reexamined claims 6 and 12-16 was merely a failed attempt to bypass the district court's *Apotex 1* invalidity judgment and prior art teachings and that appellants cannot now claim the district court's methodology is the reason for their failings. Appellees argue that the district court did not err by declining to repeat the identical reasoning for identical factual findings that appellants never appealed in *Apotex 1*. Appellees note that appellants' singular focus at trial was the 0.01 w/v% EDTA for corneal permeability and that appellants never raised the arguments rejected in *Apotex 1*, or new arguments outside this issue. Thus, appellees argue, the district court properly declined to "find" anew facts appellants did not dispute at trial or those already found and not appealed in *Apotex 1* because such facts are undisputed. Nevertheless, appellees point out that the district court properly made new fact findings specific to the reexamined claims as a whole, even beyond the 0.01 w/v% EDTA issue appellants pursued at trial, repeating a complete obviousness analysis for each claim appellants asserted, and supporting all of its findings with evidence of record from this case.

In support of their position that the district court used the predecessor claims as prior art to the present claims and failed to analyze the reexamined claims holistically, appellants cite *Interconnect Planning Corp.*, 774 F.2d 1132. In *Interconnect*, we held that the district court improperly weighed the changes in the reissue claim against the original claim and failed to consider the differences between the prior art and the reissue claim as a whole. *Id.* at 1137. This case is distinguishable from the present case. Contrary to appellants' characterization, the district court in the present case did not handpick limitations in the reexamined claims to analyze.

Instead, the district court focused on appellants' own arguments, which highlighted key claim limitations that distinguished the reexamined claims from the prior art generally.

We conclude that the district court properly considered as a whole all of the limitations in appellants' amended and newly-added claims, including "using 0.3 w/v% to 0.8 w/v% gatifloxacin;" a "pH of above 5 to about 6;" and "using 0.01 w/v% EDTA," including "to increase corneal permeability" in the context of the prior art. Specifically, the district court stepped through the disputed claim limitations and pointed out where each is found in the prior art, along with the reasoning for combining the prior art to reach the disclosure in the asserted claims. *See, e.g.*, J.A. 25-34.

Moving on to the conclusion of obviousness by the district court, we address first the obviousness of claims 12-16, the composition claims, and then the obviousness of claim 6, a method claim. The four prior art references from the *Apotex 1 & 2* cases, U.S. Patent Nos. 4,551,456 ("the '456 patent"), 4,780,465 ("the '465 patent"), and 4,980,470 ("the '470 patent"), and Grass 1985[4], are again at issue in this case.

The earliest of the prior art patents, the '456 patent, issued on November 5, 1985, teaches that then-known quinolones are both "compatible with ocular tissue" and useful in treating bacterial ocular infections through topical administration. '456 patent, 1:13-17. The '456 patent also discloses an exemplary ophthalmic composition that comprises an aqueous solution of 0.3 w/v%

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[4] "Grass 1985" is Grass et al., *Effects of Calcium Chelating Agents on Corneal Permeability*, 26 Investigative Ophthalmology & Visual Science 110 (1985). J.A. 2707-10.

norfloxacin and 0.01 w/v% EDTA, as well as the use of EDTA as one of 8 conventional excipients. *Id*. at 2:5-10.

The '465 patent, issued on October 25, 1988, discloses aqueous compositions for the quinolone lomefloxacin, also characterizing EDTA as a conventional excipient. '465 patent, 2:31-46. The '465 patent describes two exemplary ophthalmic compositions, similar to the ophthalmic composition disclosed by the '456 patent, containing 0.3 w/v% lomefloxacin and 0.01 w/v% EDTA. *Id*. at 4:1-23.

The '470 patent, issued on December 25, 1990, teaches that gatifloxacin represents an improvement over the prior art quinolones in that it exhibits a broader antibacterial activity, higher selective toxicity and safe oral and parenteral administration. '470 patent, 1:32-61. The '470 patent also teaches that each of the disclosed quinolones have "similar substituents," *id.* at 1:41-43, and that pharmaceutical formulations of gatifloxacin follow "the routes well known" with respect to "oral[ ] and parenteral [ ]" administration, including "liquids [and] eye drops." *Id.* at 7:21-26.

The Grass 1985 reference is directed to the study of EDTA's impact on the permeability of organic and inorganic compounds with respect to the corneal epithelia. J.A. 2707. Grass 1985 teaches that EDTA can reduce the number of calcium ions through chelation, thus creating small channels between corneal epithelial cells, which allow polar molecules to penetrate through the cornea into the aqueous humor of the eye. Grass 1985 specifically reports that the addition of 0.5 w/v% EDTA to separate solutions of glycerol and cromolyn resulted in increased corneal permeability in both solutions. A lower unspecified concentration of EDTA was also shown to function in this manner, albeit to a lesser extent.

In addition to these four references, appellees also raise the Grass 1988-I[5], Grass 1988-II[6], and Rojanasakul[7] references, mainly to address the additional claim limitations in the narrower, reexamined claims. The Grass 1988-I and Grass 1988-II references build on the work in Grass 1985 (collectively, "Grass references"), testing lower concentrations of 0.1, 0.05, and 0.01 w/v% EDTA, finding increased corneal permeability at these lower concentrations. The Rojanasakul reference is directed to studying the promoting mechanisms of various penetration enhancers, including EDTA, in the cornea, as well as to developing methods for evaluating tissue damage and viability. J.A. 2788. This reference builds further on the teachings of the Grass references by testing EDTA concentrations as low as 0.00037 w/v% EDTA, and finding that even these very low concentrations increased corneal permeability to some degree. J.A. 2795-96.

Appellants also raise two additional references, the Mitra reference and the Kompella reference, as evidence of nonobviousness. The Mitra reference is a comprehensive review of ophthalmic drug delivery systems. J.A. 2768-72. The Mitra reference specifically studies the mechanisms of EDTA for corneal drug penetration exam-

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[5] "Grass 1988-I" is Grass et al., *Mechanisms of Corneal Drug Penetration 1: In Vivo and In Vitro Kinetics*, 77 Journal of Pharm. Sciences 3 (1988). J.A. 2773-84.

[6] "Grass 1988-II" is Grass et al., *Mechanisms of Corneal Drug Penetration II: Ultrastructural Analysis of Potential Pathways for Drug Movement*, 77 Journal of Pharm. Sciences, 15 (1988). J.A. 2800-08.

[7] "Rojanasakul" is Rojanasakul et al., *Mechanisms of action of some penetration Enhancers in the Cornea: Laser Scanning Confocal Microscopic and Electrophysiology Studies*, 66 Int'l Journal of Pharm., 131 (1990). J.A. 2787-98.

ining the concentrations at which increases in permeability of the cornea occur. J.A. 2772. The Kompella reference is a peer-reviewed abstract that reinforces the teachings of Mitra, studying the impact of EDTA on corneal permeability. J.A. 2810-11.

First, appellants argue that the seven prior art references relied upon by the district court predate the claimed invention by at least eight years, which, "is itself evidence of nonobviousness." Appellant Br. 25 (citing *Panduit Corp. v. Dennison Mfg. Co.*, 810 F.2d 1561, 1577 (Fed. Cir. 1987)). Second, appellants argue that the district court misconstrued the teachings of the prior art. Specifically, with respect to claims 12-16, appellants argue that a skilled artisan would not have been motivated to cherry-pick individual limitations from the '456, '465, and '470 patents and combine them to achieve the compositions of claims 12-16. Appellants argue that the district court erred in selectively excerpting teachings from these three prior art references to reverse-engineer the claimed invention. In its analysis, appellants argue, the district court failed to consider whether an ordinary practitioner would have had a reason to make the multiple selections, combinations, and modifications needed under its analysis to arrive at the claimed compositions.

Appellants also argue that the district court improperly declined to consider evidence on corneal permeability with reference to the composition claims. Appellants point out that corneal permeability is relevant to these claims because the claimed compositions embody the method of reexamined claim 6 and the purpose of the composition and the functions of its limitations cannot be divorced from the obviousness inquiry. Appellant Reply Br. 19 (citing *Leo Pharmaceutical Products, Ltd. v. Rea*, 726 F.3d 1346, 1353, 1356 (Fed. Cir. 2013)). Because, according to appellants, no prior art disclosed 0.01 w/v% EDTA as preferred for the purpose of raising corneal permeability, appellants argue that they did more than

merely seek to patent a combination of known ingredients to achieve established functions.

Appellants argue that the district court improperly found claims 12-16 obvious without finding that the '456, '465, and '470 patents actually teach any gatifloxacin formulations for ocular administration. Appellants argue that the district court improperly surmised that the '456 patent teaches that quinolones are useful in treating bacterial infections, the '465 patent teaches that EDTA is a conventional excipient for use with the quinolone lomefloxacin, and the '470 patent teaches that gatifloxacin formulations can be used in known routes of oral and parenteral administration, including liquid eye drops.

Based on these conclusions, appellants argue that the district court then improperly relied on the fact that gatifloxacin is a member of the quinolone family of compounds to combine the '456 and '470 patents and arrive at the idea of an ophthalmic gatifloxacin solution, pulling teachings of gatifloxacin concentrations and pH from the '456 and '465 patents and 0.01 w/v% EDTA from the '456 patent to arrive at the specific ranges recited in the claims. Essentially, appellants argue that the district court selectively excerpted teachings from each of the three prior art patents to improperly reverse-engineer the claimed invention. Appellants point out that this is improper hindsight bias because the '456, '465, and '470 patents themselves do not disclose anything about corneal permeability of gatifloxacin solutions and, therefore, provide no reason to arrive at the claimed compositions. Appellants argue that the district court failed to identify any reasons for a skilled artisan to combine the prior art to achieve the claimed invention, finding only that a skilled artisan would have been motivated to use gatifloxacin and EDTA together and that the claimed pH and EDTA concentration limitations are found in the prior art.

Appellees respond that, with respect to claims 12-16, not only did appellants waive the issue of the years between the publication of the prior art and the filing date of the '045 patent application being "itself evidence of nonobviousness" by raising this issue for the first time on appeal, but also that the *Panduit* case appellants cite in support of their position is not comparable to the current case. Appellees point out that in the *Panduit* case, there were no prior art references at issue that disclosed or suggested all of the claimed structural limitations, while in this case several prior art references do just that. Appellee Br. 38 (citing *Panduit*, 810 F.2d at 1577).

With respect to appellants' main obviousness arguments, appellees point out that because the composition claims do not contain the corneal permeability limitation found in method claim 6, the corneal permeability teaching away arguments are irrelevant to claims 12-16. Appellees argue that the only composition element appellants deemed missing from the '456 and '465 quinolone ophthalmic formulation patents was an express mention of gatifloxacin for improving corneal permeability of any drug. Appellees argue, however, that when combined with the '470 patent, this limitation of the claims is obvious. Additionally, appellees argue there was sufficient reason to combine the claims in these three patents to render the asserted claims obvious.

Appellees characterize the '456 patent as teaching using norfloxacin and structurally related antibodies in topical ocular formulations, while the '465 patent taught preparing stable ophthalmic fluoroquinolone compositions, with both patents containing ingredient ranges encompassing those claimed. Both the '456 and '465 patents also taught topical ocular formulations containing various features encompassed by the composition claims, such as 0.01 w/v% EDTA and 5.2 pH. Because the art viewed gatifloxacin as an improved fluoroquinolone, appellees argue that one of ordinary skill in the art would

have had reason to combine the '470 patent's gatifloxacin disclosure to improve the '456 and '465 patents' formulations.

Appellees also argue that these disclosures combined with appellants failure to dispute that the art viewed gatifloxacin as an improved fluoroquinolone, provides the reason why one of ordinary skill would want to improve the '456 and '465 patents by incorporating the '470 patent's gatifloxacin. Appellees point out that the '470 patent's gatifloxacin eye drop teaching is directed to the same drug class as the '456 and '465 patents and provides evidence that gatifloxacin should work in the '456 patent's formulation.

With respect to claims 12-16, we conclude that the district court properly held these claims obvious. Appellants' argument relating to the eight year gap between the prior art and the filing of the '045 patent application is unconvincing and not properly raised. Appellants only show of support for this issue being raised prior to this appeal is a single citation to the district court opinion in which appellants argue, in a footnote, that the district court "acknowledged the vintage of the prior art," citing to portions of the district court opinion that merely recite the years in which the prior art was published. Appellant Br. 19 n.4 (citing J.A. 10-14). This is insufficient discussion to consider this argument raised at the district court, and this argument is, therefore, waived. *See Sage Prods., Inc. v. Devon Indus., Inc.*, 126 F.3d 1420, 1426 (Fed. Cir. 1997) (finding that "[w]ith few notable exceptions . . . appellate courts do not consider a party's new theories, lodged first on appeal").

For the purpose of claims 12-16, the main focus of appellants' appeal brief was on the inclusion of the corneal permeability limitation in the analysis of the validity of these claims. We conclude that the district court properly found that corneal permeability is not relevant in the

discussion of composition claims 12-16 because these claims do not contain the corneal permeability limitation found in method claim 6, discussed below. J.A. 24 n.25.

We do not find persuasive appellants' argument that it is necessary to consider corneal permeability when analyzing claims 12-16 because the claimed compositions embody the method of reexamined claim 6. The *Leo Pharmaceutical Products, Ltd. v. Rea*, 726 F.3d 1346, 1349-50 (Fed. Cir. 2013), case appellants cite in support of their argument examines a composition claim that includes as a limitation the function of the composition. In composition claims 12-16 of the '045 patent, there is no limitation denoting the function of the composition and we decline to import this limitation into the claims. *See Phillips v. AWH Corp.*, 415 F.3d 1303, 1323 (Fed. Cir. 2005) (stating that we have repeatedly warned against confining the claims to particular embodiments in the written description).

Further, there were several other factors in *Leo Pharmaceutical* that led the court to conclude that the claims were nonobvious, including a lack of reasons for one of ordinary skill in the art to combine the asserted prior art references. *Leo Pharm.*, 126 F.3d at 1354. In the present case, there were sufficient reasons to improve upon the '456 and '465 patents by utilizing gatifloxacin, as disclosed in the '470 patent, and described fully below. All three of these patents relate to quinolones and their derivatives for use as antibacterial agents, and we conclude that the district court properly determined that combining them would have been obvious to one of ordinary skill in the art.

The '045 and '456 patents disclose ophthalmic quinolone compositions in topical ocular formulations, which gave reasons to one of ordinary skill in the art to combine with the gatifloxacin disclosure of the '470 patent because gatifloxacin was recognized in the art as an improved

fluoroquinolone. Appellants never disputed that the art viewed gatifloxacin as an improved fluoroquinolone. Thus, it would have been obvious to improve the '456 and '465 patent formulations by incorporating the '470 patent's gatifloxacin.

Many of appellants' arguments on the lack of reasons to combine the teachings of these three patents rely on the fact that they do not disclose anything about corneal permeability of gatifloxacin solutions. As discussed above, this is not a limitation of claims 12-16 and, therefore, is not relevant to the obviousness determination.

Lastly, the use of gatifloxacin with EDTA would have been obvious to a person of ordinary skill in the art. EDTA is listed among eight "conventional ingredients" in the '456 patent and a similar group of excipients. '456 patent, 2:1-16; '456 patent, 2:36-49. Further, the use of 0.3 to 0.8 w/v% of gatifloxacin is outlined in the prior art, such as in the '456 patent, 1:37-43 ("from about 0.03 to 3%"), and in the '465 patent, 2:22-25 ("preferably about 0.3% to 5% w/v"). As the district court pointed out the use of 0.01 w/v% EDTA was also known from the '456 patent, which discloses an exemplary formulation of 0.3% quinolone solution that incorporates 0.01 w/v% EDTA, and teaches using "from about 0.03 to 3% and especially 0.15% to 0.6% of medicament although higher or lower dosages can be employed." '456 patent at 1:37-40, 4:1-23.

Based on the foregoing, we conclude that the district court properly held that claims 12-16 were invalid as obvious.

Next, we analyze whether method claim 6 would have been obvious. In general, appellants argue that the district court improperly found that all of the features of claim 6 of the '045 patent are disclosed in the prior art, and that appellees failed to prove invalidity of claim 6 by clear and convincing evidence. Specifically, appellants argue that nothing in the prior art reasonably suggested

that the claimed limitations of 0.01 w/v% EDTA at pH 5-6 would have *any* effect in improving gatifloxacin's corneal permeability *in vivo*. In fact, appellants argue, the prior art expressly taught that these claimed limitations would have no effect on corneal permeability.

Appellants argue that several prior art references which teach away from the claimed invention, including the Mitra and Kompella references, are notably absent from the district court's invalidity analysis. Appellants argue that the district court's boilerplate language stating that it had "considered the documentary evidence and testimony" is insufficient to discharge the challenger's burden of proving obviousness. Appellant Reply Br. 3 (citing *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1075, 1077 (Fed. Cir. 2012)). Appellants argue that, by addressing only those references that, in the view of the district court, pointed towards obviousness, the district court failed to weigh all of the evidence on both sides of the question of invalidity.

Appellants argue that the prior art taught the use of high EDTA concentrations to increase corneal permeability, not the use of low EDTA concentrations, such as those disclosed in the '045 patent. For example, appellants argue that in the Kompella reference, researchers used EDTA at a concentration of 0.5 w/v%, fifty times that of the '045 patent, to increase corneal permeability of several beta-blockers, while also teaching that increasing pH to 8.4—well above the claimed pH range of 5-6—improved corneal permeability. Appellants further argue that the Mitra reference expressly discouraged seeking to improve corneal permeability using the claimed EDTA concentration *in vivo*, reporting that such concentrations are "devoid of any effects" in *in vitro* experiments. Thus, appellants argue, both Mitra and Kompella suggest a line of development pointing towards higher EDTA concentra-

tions and higher pH levels to increase corneal permeability—and thus away from the claimed invention.

Appellants also argue that the Grass references do not render claim 6 obvious. Specifically, appellants argue that Grass 1985 did not study the corneal permeability of gatifloxacin or any quinolone, nor did it employ concentrations and conditions resembling those specified in the reexamined claims. Further, appellants argue that Grass 1988-I explicitly reported that 0.01 w/v% EDTA has "0" effect on corneal permeability *in vitro*, reporting the results for 0.01 w/v% EDTA statistically indistinguishable from zero. Appellants argue that the district court improperly focused on the Grass 1988-I raw data to find increased permeability even though the percentage change was reported as zero.

Appellants further argue that the district court's reliance on the Rojanasakul reference was misplaced. Appellants point out that Rojanasakul did not measure the passage of any molecule through the corneal membrane, rather, Rojanasakul measured changes in the electrical resistance of corneal tissue, using electrical resistance as a general proxy for membrane permeability of ions. According to appellants, appellees did not deny that Rojanasakul did not measure the corneal permeability of any molecule, relying only on attorney argument to support its position that a person of ordinary skill in the art would have expected electrical resistance to correlate with the corneal transport of gatifloxacin based on Rojanasakul. Further, appellants argue that the district court misconstrued Rojanasakul, which uses "permeability" to refer not only to the permeability of the corneal membrane comprising the surface of the eye, but also to permeability of the plasma membrane surrounding individual cells. Thus, the increase in permeability disclosed in Rojanasakul is not applicable to the asserted claims.

Appellants argue that because none of the '456, '465, and '470 patents even mention corneal permeability, these prior art patents would not have provided a reason for a skilled artisan to seek improved corneal permeability using low EDTA concentrations. Appellants argue that if it was as simple as incorporating gatifloxacin into existing formulations, as appellees contend, this invention would have likely been achieved within months as opposed to the eight years that passed before anyone conceived the claimed compositions. Appellants argue that the inclusion of EDTA among the possible excipients mentioned in the '456 and '465 patents does not render its eventual use in raising corneal permeability of gatifloxacin unpatentable, because the asserted claims, at a minimum, present a new way of using an existing drug.

Lastly, appellants argue that the prior art taught the use of higher pH, not lower pH, to improve corneal permeability. Appellants argue that the prior art uniformly taught using pH levels higher than the claimed range of 5-6, citing Grass 1985 (pH 7.4), Grass 1988-I (pH 7.4-7.6), Grass 1988-II (pH 7.4), Kompella (pH 8.4), and Rojanasakul (pH 7.4). Appellants point out that the only evidence appellees have of a change in permeability is a decrease in permeability when lowering the pH, not an increase in permeability with a decrease in pH as claimed in the patent. Thus, appellants argue that the evidence confirms the surprising nature of the inventors' discovery that 0.01 % w/v% EDTA formulations significantly increase gatifloxacin concentrations in the aqueous humor, even at relatively low pH levels.

Appellees respond that appellants' experts offered no opinions defending the non-obviousness of the claim elements relating to pH, gatifloxacin percentages, use of isotonic agents, or the combination thereof in an ophthalmic formulation. Instead, appellees argue, appellants' expert opined solely upon the question of whether one of ordinary skill would expect 0.01 w/v% EDTA to work to

increase corneal permeability. Thus the district court correctly found that all of the features of the asserted claims of the '045 patent are disclosed in the prior art.

Appellees argue that the district court was not obligated to cite the Kompella and Mitra references in its opinion. Appellee Br. 45 (citing *MySpace, Inc. v. GraphOn Corp.*, 672 F.3d 1250, 1263-64 (Fed. Cir. 2012); *Plant Genetic Sys., N.V. v. DeKalb Genetics Corp.*, 315 F.3d 1335, 1343 (Fed. Cir. 2003)). Appellees point out that the district court explained that it considered the documentary evidence and testimony, along with the parties' post-trial briefing, which discussed both of these references. Thus, appellees argue, the references were presumptively considered.

Further, appellees argue that neither the Kompella or Mitra references teach away from the claimed invention. According to appellees, the Kompella reference says nothing derogatory about 0.01 w/v% EDTA or lower pH ranges, never even testing or commenting on 0.01 w/v% EDTA formulations. Appellees also argue that the Mitra reference nowhere discourages investigation or dissuades the development of 0.01 w/v% EDTA formulations for polar drugs, such as gatifloxacin, which has an ability to readily ionize and contains several polar moieties. J.A. 10. In fact, appellees argue, appellants mischaracterize the disclosure in Mitra that 0.2 and 5 mM EDTA doses are devoid of any effects, omitting the important fact that the numbers for these tests were with a different compound, even without EDTA, that had no transport across the membranes. Appellees argue that Mitra supports Grass's teachings that a range of EDTA levels increased corneal permeability, recognizing that an EDTA drug combination deserves some consideration in improving the bioavailability of poorly penetrating drugs. Appellee Br. 16 (citing J.A. 2772).

Appellees add that Grass 1985 taught the broad effect of EDTA's corneal permeability-increasing properties, recognizing that since "chelating agents are added routinely to ophthalmic medications for stability purposes," the results of the Grass tests would have a "direct bearing upon ophthalmic solutions currently in use" even though such solutions used EDTA amounts "at lower concentrations." Appellee Br. 10-11 (citing J.A. 2707, 2709-10). Appellees also argue that appellants mischaracterize the Grass 1988-I and Grass 1988-II references as establishing a 0.01 w/v% threshold where EDTA's effect on corneal permeability was zero. Instead, as Lupin's expert explained, it is appellees position that the art showed the skilled person that "EDTA works at exceedingly low concentrations" and did not "magically start" at a specific number. Appellee Br. 12-13 (citing J.A. 1695). Appellees further point out that there is no support for appellants' argument that the "0" assigned to the 0.01 w/v% EDTA numbers in Table XIII of Grass 1988-I means that the measured result is unreliable. Instead, appellees argue, this "0" simply signifies that the data did not reach statistical significance, even though one of ordinary skill reading Grass 1988-I observed raw data confirming an actual measured increase of corneal permeability, even at 0.01 w/v% EDTA levels.

As characterized by appellees, Senju's arguments with respect to Rojanasakul include a variety of uncited attorney characterizations about the reference's teachings that no trial witness offered. Appellees point to Rojanasakul's teaching that changes in electrical resistance and capacitance correlate well with changes in the aqueous intercellular space and membrane surface integrity, respectively, to support the relevance of Rojanasakul's finding that electrical resistance changed after being exposed to EDTA levels as low as 0.00037 w/v%. Because appellants admit that intercellular space is the space between cells through which gatifloxacin travels, appellees argue that a person

of ordinary skill in the art could reasonably conclude that even very low EDTA levels would impact the cellular junctions, thereby promoting transport of gatifloxacin.

With respect to claim 6, we conclude that the district court properly held this claim invalid as obvious in light of the '456, '465, and '470 patents, along with the Grass 1985, Grass 1988-I, Grass 1988-II, and Rojanasakul references.[8] We find that the district court applied correct legal standards, accepting that the '045 patent was entitled to a presumption of validity; that appellees had to establish the underlying factual proofs of obviousness by clear and convincing evidence; and that the court properly considered all of the relevant evidence. *See Sciele Pharma Inc. v. Lupin Ltd.*, 684 F.3d 1253, 1260 (Fed. Cir. 2012) ("Whether a reference was previously considered by the PTO, the burden is the same: clear and convincing evidence of invalidity.").

Though the district court did not specifically cite to Kompella and Mitra in its opinion, this is not fatal because neither the Mitra nor the Kompella reference actually teach away from utilizing a lower EDTA concentration at the claimed pH level. While both references find success at higher EDTA concentrations, they do not provide any indication that lower EDTA concentrations would not also work. *See* J.A. 2811, 2772. Because the district court was not required to directly address these references and the references do not provide evidence of teaching away from the '045 patent disclosure, the district court did not commit clear error in its analysis. *See*

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[8] With regard to appellants' "size-dependent" theory, it was untimely because appellants provided no evidence that they alleged gatifloxacin's size precluded movement through EDTA-created intercellular spaces. The district court properly excluded this argument as untimely and we decline to address it further.

MySpace, Inc., 672 F.3d at 1263 (finding that "[w]here the record adequately supports the judgment, the district court does not have an obligation to recite every detail of its reasoning") (citing *Lexion Med., LLC v. Northgate Techs., Inc.*, 641 F.3d 1352, 1359 (Fed. Cir. 2011)).

Appellants focus on the use of 0.01 w/v% EDTA to increase corneal permeability as the distinguishing feature of claim 6. However, this feature does not sufficiently distinguish claim 6 from the prior art. The asserted references demonstrate that one of ordinary skill in the art would have known that using 0.01 w/v% EDTA would result in an increase in corneal permeability. Specifically, we look to Grass 1985, which suggests that EDTA concentrations lower than 0.5 w/v% would be effective in view of the increased corneal permeability of the 0.5 w/v% EDTA formulation to which calcium was added. J.A. 2710. This disclosure in Grass 1985 would lead one of ordinary skill to apply this teaching in conjunction with the pre-existing quinolone formulations, which incorporated between 0.05 and 0.1 w/v% EDTA, in arriving at a gatifloxacin formulation characterized by increased corneal permeability. *See*, *e.g.*, J.A. 2712-13.

Contrary to appellants' arguments that the prior art teaches that the use of 0.01 w/v% EDTA fails to increase corneal permeability of either of the polar compounds tested, the prior art actually teaches that adding EDTA to any polar compound will increase corneal permeability dose-dependently. For example, after experimenting with higher concentrations, Grass 1988-I tested 0.1, 0.05, and 0.01 w/v% EDTA, finding that each concentration raised corneal permeability, even though not all of the increases were statistically significant. J.A. 2780. Appellants improperly focus on the percentage change in permeability over the control, which was zero for both methanol and glycerol, to conclude that the data showed no increase in corneal permeability. In reality, though the percent changes were not statistically significant, appellees set

forth expert testimony that a person of ordinary skill would have recognized from the data that 0.01 w/v% EDTA would increase corneal permeability. J.A. 1695. This testimony is consistent with other prior art, such as Rojanasakul, which confirmed a dose dependent relationship between EDTA concentration and corneal permeability, testing concentrations of EDTA as low as 0.00037 w/v%. J.A. 2795-96. Thus, the prior art suggests that the use of concentrations as low as 0.01 w/v% EDTA would be effective to increase corneal permeability.

At bottom, the district court's analysis rests largely on a determination that Lupin's experts were more credible than Senju's experts. J.A. 30-31. Based on this determination, the district court found that Grass 1988-I, along with the other cited references, taught that 0.01 w/v% EDTA would be effective to increase corneal permeability. J.A. 31. On the evidence before us, that determination by the district court falls well within the wide discretion the court has to weigh expert credibility. Ordinarily, and absent compelling reason otherwise, an appellate court defers to such credibility determinations. *See Celsis In Vitro, Inc. v. CellzDirect, Inc.*, 664 F.3d 922, 929 (Fed. Cir. 2012).

2. *Unexpected Results*

Appellants argue that the district court engaged in an improper *post hoc* analysis of appellants' evidence of unexpected results, concluding that the claims were obvious before fully considering evidence of unexpected results and without making any finding of the results a skilled artisan would have expected. Appellants point out that a complete administrative record—including the Senju studies and the Grass 1985 and Grass 1988-I references—was before the PTO at the reexamination and that the examiners' decision to grant the amended and new claims "'carries with it a presumption that [each] Examiner did his duty and knew what claims he was

allowing.'" Appellant Br. 53 (citing *Al-Site Corp. v. VSI Int'l, Inc.*, 174 F.3d 1308, 1323 (Fed. Cir. 1999) (quoting *Intervet Am., Inc. v. Kee-Vet Labs., Inc.*, 887 F.2d 1050, 1054 (Fed. Cir. 1989))). Thus, appellants argue, the district court erred in failing to give weight to the PTO's factual findings on validity and unexpected results.

Appellants argue that two pre-litigation studies conducted by Senju in 2006 (the "'901 study" and the "'904 study") measured and compared corneal concentrations of gatifloxacin after administering the compound in solutions with and without EDTA, demonstrating the expected and surprising benefits of the claimed invention. Appellants expound that these studies provide undisputed results demonstrating that the addition of 0.01% w/v% EDTA results in a 27-40% increase in gatifloxacin in the aqueous humor. The Grass 1988-I reference, appellants argue, reported a zero percent change in permeability of glycerol upon addition of 0.01 w/v% EDTA *in vitro*, and the Grass 1988-II article taught that concentrations of EDTA about 0.01 w/v% were needed *in vitro* to show an effect on corneal permeability of glycerol. Appellants point out that even if Grass 1998-I was interpreted as teaching some miniscule increase in corneal permeability of gatifloxacin with 0.01 w/v% EDTA, the sheer magnitude of improvement observed in Senju's '901 and '904 studies would have been unexpected and surprising.

Appellants further argue that appellees presented no evidence that anyone in 1998 would have expected a low concentration of EDTA to produce a significant increase in gatifloxacin's corneal permeability. In fact, appellants argue, the remainder of the prior art references, including Grass 1985, Mitra, and Rojanasakul, reinforce the surprising results of Senju's '901 and '904 studies, as none of these references suggest that the claimed EDTA concentration would result in an increase in aqueous humor concentrations of glycerol and cromolyn. Additionally, the prior art uniformly taught using pH levels higher than

the claimed range of 5-6, confirming the surprising nature of the inventor's discovery that 0.01 w/v% EDTA formulations significantly increase gatifloxacin concentrations in the aqueous humor even at relatively low pH levels.

Appellees respond that the district court properly found the claims obvious only after considering appellants' unexpected results evidence and finding it unpersuasive. Despite Senju setting forth a persuasive case before the Examiner at the USPTO, their theories collapsed before the district court. Appellees point out testimony from appellants' expert who testified that the '901 study did not show the gatifloxacin-0.01 w/v% EDTA solution produced corneal permeability benefits that were statistically significant compared to a non-EDTA solution. Appellees argue that the district court heard testimony from both experts, weighed their credibility, and reviewed Grass 1988-I as a whole before finding more credible Lupin's expert's opinions that the skilled person would not interpret Grass 1988-I as teaching "no increase" occurred at 0.01 w/v% EDTA.

Appellees also argue that the raw data reported in Grass 1988-I shows that numerically, the corneal permeability levels did increase compared to control even with the 0.01 w/v% EDTA formulations. Appellees point out that the 27 and 40% permeability increase numbers in the raw data appellants rely on for evidence of unexpected success occurred in studies where all of the numbers (including control values) widely varied, with large, unexplained error bars. Appellees argue that if a mere pH adjustment of one unit can produce a 30% difference in corneal permeability, and pH adjustments are routinely done, appellants' 27-40% change in corneal permeability with 0.01 w/v% EDTA has a magnitude achievable by other formulation tweaks and routine practice. Further, appellees argue, the district court properly found that achieving changes on this order of magnitude reflected the "product of routine optimization." J.A. 33-34.

Appellees argue that the district court properly found the unexpected results evidence unpersuasive because the results of the '901 and '904 studies were not statistically significant and merely reported numerical increases that were unsurprising in light of Grass 1988-I. Appellees point out that Dr. Grass only acknowledged that the Senju '901 study reports a single time point that the study claimed was statistically significant, but that Lupin's statistician demonstrated this time point was statistically insignificant under a correct analysis. Appellees argue that Senju's studies achieved nothing better than Grass 1988-I in which 0.01 w/v% EDTA solutions were tested as single doses and showed concentration and time dependence where the 30 minutes' permeability numbers quadrupled or more than the 20 minute permeability numbers.

We conclude that the district court properly considered evidence of unexpected results, J.A. 32-34, and did not err in finding that, based on the record and testimony offered, the increase in corneal permeability shown by plaintiffs using a 0.01 w/v% EDTA is not unexpected or surprising, but is a product of routine optimization that would have been obvious to one of skill in the art. J.A. 33-34. These determinations, much like many of the obviousness determinations, were based on credibility judgments on which, on the evidence before us, we defer to the district court. *See Celsis In Vitro*, 664 F.3d at 929.

We further conclude that the district court properly applied a presumption of validity, considering both the evidence of obviousness and the evidence of unexpected results, to find that appellees set forth clear and convincing evidence of invalidity in this case. *See Sciele Pharma Inc.*, 684 F.3d at 1260. We agree that it was not clear error for the district court to conclude that the unexpected results evidence that Senju relied upon during reexamination, J.A. 2692, did not withstand scrutiny by Lupin's experts and the district court. Ultimately, the district court properly concluded that the theories presented

during reexamination proved too weak when challenged in a judicial forum to rise to the level of unexpected results sufficient to rebut a strong case of obviousness. *See Proctor & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009).

We have considered and find unpersuasive the remainder of appellants' arguments. Concluding that the district court did not err in its judgment that the reexamined claims at issue are invalid for obviousness, we need not reach the issues of infringement and estoppel.

III. CONCLUSION

The judgment of the district court is affirmed.

AFFIRMED

United States Court of Appeals for the Federal Circuit

SENJU PHARMACEUTICAL CO., LTD., KYORIN PHARMACEUTICAL CO., LTD., ALLERGAN, INC.,
Plaintiffs-Appellants

v.

LUPIN LIMITED, LUPIN PHARMACEUTICALS, INC.,
Defendants-Appellee

HI-TECH PHARMACAL CO., INC.,
Defendant-Appellee.

2013-1630

Appeals from the United States District Court for the District of Delaware in Nos. 11-CV-0271, 11-CV-0439, 11-CV-0926, 11-CV-1059, Judge Sue L. Robinson.

NEWMAN, *Circuit Judge*, dissenting.

In prior litigation, the district court held Senju's patent claims invalid on the ground of obviousness. Before that decision reached finality, Senju requested PTO reexamination, presenting new claims of significantly narrowed scope. The PTO reexamined Senju's U.S. Patent No. 6,333,045 ("the '045 patent"), and held the narrowed claims patentable. In this subsequent litiga-

tion, the district court gave no deference to the PTO's review of the restricted claim scope or the unexpected results at that scope, and held the narrowed claims invalid on the same grounds it previously applied to the original claims.[1]

My colleagues on this panel repeat that flawed analysis: they do not consider the scope of the reexamined claims, the unexpected results at that scope, and the teaching-away of the prior art. I respectfully dissent, for these claims have not been shown to be invalid.

DISCUSSION

The Senju inventors discovered that a composition containing the antibiotic gatifloxacin enhances corneal permeability when combined with very low amounts of ethylenediaminetetracetic acid (EDTA) at a specific pH. This is the appellants' Zymar® product, whose commercial and medicinal success is the impetus for this Hatch-Waxman Act challenge to Senju's patent.

The prior art is crowded. It contains much data on quinolones, the family of which gatifloxacin is a member. The prior art also shows the use of chelating agents, such as EDTA, as excipients that enhance stability of ophthalmic medications. However, no combination of prior art references shows or suggests the use of very low concentrations of EDTA to enhance the corneal permeability of antibiotic formulations of gatifloxacin, or of any other quinolone.

In this crowded field, the specific combination and concentration here claimed is not shown, and the published scientific data lead away from the claimed subject

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[1] *Senju Pharm. Co., Ltd. v. Lupin Ltd.*, Civ. No. 11-271-SLR, 2013 WL 4101820 (D. Del. Aug. 9, 2013) ("Dist. Ct. Op.").

matter. These inventors discovered that, when using EDTA at a concentration of 0.01 w/v%, the formulation is not only effective as an antibiotic, but, contrary to the prior art, increases the corneal permeability of gatifloxacin.

I focus specifically on reexamined claim 6:

> 6. A method for raising corneal permeability of an aqueous pharmaceutical Gatifloxacin eye drop solution comprising Gatifloxacin or its salt, having a pH of from above 5 to about 6 containing from about 0.3 to about 0.8 w/v% Gatifloxacin or its salt, which comprises incorporating about 0.01 w/v% disodium edetate into [eye drops containing Gatifloxacin or its salt] said Gatifloxacin eye drop solution.

'045 patent, col. 1 l. 25–col. 2 l. 5.

During reexamination, the PTO examiner found that no reference or combination of references teaches or suggests the improved corneal permeability obtained using EDTA at the low concentration of 0.01 w/v%. The prior art experimental data show either no effect at 0.01 w/v% or enhanced permeability at concentrations above 0.01 w/v%.

No reference shows improved corneal permeability at such low concentrations of EDTA; all indications are that the EDTA concentration should be above 0.01 w/v%. The Senju discovery contradicts the observations reported in the prior art. Nonetheless, the panel majority holds that it was obvious that superior results would be obtained by reducing the concentration.

The Grass et al. Scientific Articles

Of primary import to the district court's opinion are three publications by Dr. George M. Grass, *et al.* The panel majority states that these publications render the

claimed combination obvious. To the contrary, these publications teach away from the direction taken by the Senju inventors.

Grass et al., Mechanisms of Corneal Drug Penetration I: In Vivo and In Vitro Kinetics, 77 J. Pharm. Sci. 3 (1988) *("Grass 1988-I")*:

The panel majority states that the Grass 1988-I reference shows that the three concentrations of EDTA tested (0.1, 0.05 and 0.01 w/v%) are effective at enhancing corneal permeability. That is incorrect. Grass 1988-I shows that EDTA at a concentration of 0.01 w/v% produced a *zero* percent increase in corneal permeability, measured for both methanol and glycerol. Grass 1988-I also states that the *in vitro* experiments were performed at exposures (3 hours) significantly longer than most topical applications would provide, yet the reported data are that EDTA at 0.01 w/v% was totally ineffective.

Grass 1988-I discusses the work of other investigators, and reports no corneal penetration of mannitol using EDTA at concentrations of 0.2 and 5 mM. Grass 1988-I concludes that corneal permeability increases with increased concentration of EDTA. This leads directly away from any suggestion or expectation of improved permeability of gatifloxacin formulations with concentrations of EDTA as low as 0.01 w/v%.

The appellees concede that Grass 1988-I shows no statistically significant increase in corneal permeability at the low concentration of 0.01 w/v%: "the data did not reach statistical significance." Appellee Br. at 13. Yet, the panel majority affirms the district court's unsupported finding that the "prior art suggests the use of concentrations as low as 0.01 w/v% EDTA would be effective to increase corneal permeability." Dist. Ct. Op. at *11. This finding is contrary to the record. The most that Grass 1988-I can be deemed to "suggest" is that the EDTA concentration should be higher than 0.01 w/v%.

The two other cited Grass publications reinforce the "teaching away" of the prior art:

Grass et al., Effects of Calcium Chelating Agents on Corneal Permeability, 26 Investigative Ophthalmology & Visual Sci. 110 (1985) *("Grass 1985")*:

Grass 1985 describes the effects of the chelating agents EDTA and Cromolyn on corneal permeability of glycerol and progesterone in rabbit eyes. Grass 1985 reports that EDTA at concentrations of 0.5 w/v% increased glycerol concentration in the aqueous humour, and concludes that the addition of chelators at high concentrations or by frequent application may increase the permeability of the corneal epithelium. This reference shows enhanced effects at higher concentrations, not the low concentration in claim 6.

Grass et al., Mechanisms of Corneal Drug Penetration II: Ultrastructural Analysis of Potential Pathways for Drug Movement, 77 J. Pharm. Sci. 15 (1988) *("Grass 1988-II")*:

Grass 1988-II describes electron microscope studies of rabbit eyes exposed to EDTA and glycerol, specifically analyzing corneal epithelial cell junctions after treatment with EDTA and glycerol. Grass 1988-II reports that the effects of EDTA depend on concentration and exposure time, and that at concentrations of 0.01 w/v% EDTA, the epithelial tissue showed no visible expansion of the intercellular spaces, which is described as correlating with corneal permeability. The authors interpret these results as showing that "in vitro concentrations of EDTA above 0.01% caused increased permeability of the cornea to glycerol." Grass 1988-II at 22.

Collectively, the Grass references show or suggest that EDTA must be used at concentrations higher than 0.01 w/v% to effectively increase corneal permeability.

OPTHALMIC DRUG DELIVERY SYSTEMS, (Ashim K. Mitra ed., Marcell Dekker, Inc., 1993) *("Mitra")*:

The Mitra book summarizes the research and knowledge in this field, and states that experiments using low concentrations of EDTA were "devoid of any effects (62), suggesting a concentration dependence." Mitra at 188. Mitra states that EDTA-drug combinations "deserve investigation," but that "[i]t seems likely that the high concentration of divalent cations in the tear film would prevent EDTA from enhancing permeability." *Id.* Mitra adds that while improving drug transport across the cornea found some success, "it is in the modification of the drug that has generated greater interest." *Id.*

The panel majority rejects the argument that Mitra teaches away from Senju's discovery, stating that Mitra does not "provide any indication that lower EDTA concentrations would not also work." Maj. Op. at 25. That is not the law of "teaching away." A reference need not foresee a later-discovered invention and warn against it, to teach away from the discovery. *Spectralytics, Inc. v. Cordis Corp.*, 649 F.3d 1336, 1343 (Fed. Cir. 2011).

A reference teaches away when it leads to a path divergent from that taken by the patentee. *Pozen, Inc. v. Par Pharm., Inc.*, 696 F.3d 1151, 1165 (Fed. Cir. 2012). Mitra explicitly sets forth two separate paths for investigation – high concentrations of EDTA and drug modification – both of which diverge from the path in claim 6. The entire body of prior art leads in the direction opposite to reducing the EDTA concentration, for the body of prior art points toward higher, not lower, concentrations of EDTA to enhance corneal permeability.

Other References

Three other references relied on by the district court (U.S. Patent Nos. 4,551,456; 4,780,465; and 4,980,470) make no mention of improving corneal permeability.

Those references describe gatifloxacin as an antibiotic and EDTA as a traditional excipient, i.e., as an inactive drug ingredient; they contain no teaching or suggestion related to corneal permeability.

The Legal Conclusion of Obviousness

Obviousness is a matter of foresight, not hindsight. A determination of obviousness requires some reason or suggestion, in the prior art or in common sense, that the claimed subject matter is likely to be effective for its intended purpose. *KSR Int'l Corp. v. Teleflex Inc.*, 550 U.S. 398, 420–22 (2007). Here, the prior art taught away from the claimed combination when it indicated that higher concentrations of EDTA are needed to enhance corneal permeability.

The panel majority relies on the unsupported opinion of Lupin's expert witness, and gives that unsupported opinion greater weight than the experimental data. Such reliance is discredited. *See Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579, 589 (1993) ("Proposed testimony must be supported by appropriate validation – i.e., 'good grounds,' based on what is known. In short, the requirement that an expert's testimony pertain to 'scientific knowledge' establishes a standard of evidentiary reliability.").

Contrary to the theory of Lupin's expert, the extensive Grass data show no statistically significant enhancement of corneal permeability in the experiments using EDTA at low concentrations, or for other chelating agents at low concentrations. The prior art did not test the specific combination of gatifloxacin and 0.01 w/v% of EDTA and did not discover the subject matter that is here claimed.

Notwithstanding the published contrary data, the panel majority calls upon judicial hindsight and finds that persons skilled in the field of the invention would have recognized that 0.01 w/v% EDTA would increase corneal

permeability of gatifloxacin formulations. However, the scientists conducting the Grass studies interpreted their data to "suggest that under conditions of sufficient calcium chelation, either by high enough concentrations of one or more chelators or frequent application at short intervals, preservatives may indeed enter anterior segment tissue." Gras 1988-I at 11. Grass suggested "high enough concentrations," not very low concentrations.

The published contemporaneous statements of scientists interpreting their experiments warrant more weight than unsupported opinions appearing for the first time in litigation. Grass did not test the composition here patented, and reported to be a product now of medical choice.

Senju's pre-litigation experiments further support the conclusion that one skilled in the art would not have expected to enhance corneal permeability using the method of claim 6. The district court acknowledged that the claimed levels of EDTA were shown in Senju's experiments to produce a significant increase in the concentration of gatifloxacin in the aqueous humour. Nevertheless, the court faulted Senju's expert because he did not use statistical analysis to show that the effects were unexpected. Statistical analysis can indeed be helpful at times, but the perspective of those skilled in the art cannot be ignored. With the exception of Lupin's expert witnesses, those skilled in the art interpreted Senju's experiments as demonstrating unexpected results.

CONCLUSION

The scientific references, the experimental record, and the commercial success all support the conclusion that the subject matter of claim 6 would not have been obvious to a person of ordinary skill at the time of the invention. The PTO on reexamination correctly applied the law of obviousness. Invalidity of reexamined claim 6 was not proved

by clear and convincing evidence. From my colleagues' contrary ruling, I respectfully dissent.