United States Court of Appeals for the Federal Circuit

INSITE VISION INCORPORATED, INSPIRE PHARMACEUTICALS, INC., PFIZER INC.,
Plaintiffs-Appellees

v.

SANDOZ, INC.,
Defendant-Appellant

SANDOZ GMBH, SANDOZ INDUSTRIAL PRODUCTS S.A.,
Defendants

2014-1065

Appeal from the United States District Court for the District of New Jersey in No. 3:11-cv-03080-MLC-LHG, Judge Mary L. Cooper.

Decided: April 9, 2015

DOMINICK A. CONDE, Fitzpatrick, Cella, Harper & Scinto, New York, NY, argued for plaintiffs-appellees. Also represented by DAVID E. DE LORENZI, Gibbons P.C., Newark, NJ. Plaintiffs-appellees Inspire Pharmaceuticals, Inc., Pfizer Inc. also represented by MARGARET A. SCOOLIDGE, Fitzpatrick, Cella, Harper & Scinto, New York, NY; DENNIS C. AELING, Costa Mesa, CA.

BRIAN ROBERT MATSUI, Morrison & Foerster LLP, Washington, DC, argued for defendant-appellant. Also represented by DEANNE E. MAYNARD; DAVID CLARENCE DOYLE, JAMES WEBB HUSTON, MARK ANDREW WOODMANSEE, SAN DIEGO, CA; MATTHEW D'AMORE, NEW YORK, NY.

Before PROST, *Chief Judge,* NEWMAN and LINN, *Circuit Judges.*

LINN, *Circuit Judge.*

In this Hatch-Waxman Act litigation, Sandoz, Inc. ("Sandoz") appeals the district court's decision in *Insite Vision, Inc. v. Sandoz, Inc*, No. 11-3080, 2013 WL 5975015 (D.N.J. Oct. 4, 2013), which held that Sandoz had not shown that the claims of U.S. Patents No. 6,861,411 (the "'411 patent"); No. 6,239,113 (the "'113 patent"); No. 6,569,443 (the "'443 patent"); and No. 7,056,893 (the "'893 patent") (collectively "the patents-in-suit") asserted by Insite Vision, Inc. ("Insite"); Inspire Pharm., Inc. ("Inspire"); and Pfizer, Inc. ("Pfizer") (collectively "plaintiffs") are invalid as obvious. This court agrees that Sandoz failed to show that the asserted claims in the patents-in-suit would have been obvious to a person of ordinary skill in the art and therefore affirms.

I. BACKGROUND

A. THE PATENTS-IN-SUIT

The '411 patent issued from U.S. Patent Application No. 09/200,199 (the "'119 application"), which was filed on November 25, 1998, claiming priority to a provisional application filed on December 2, 1997. It is owned by Pfizer. Insite owns the '113, '443 and '893 patents (the "ISV patents"). The ISV patents claim priority to an application filed on March 31, 1999. Inspire is the exclu-

sive sub-licensee of the '411 patent and the exclusive licensee of the ISV patents.

The '411 patent discloses methods of treating eye infections by the topical administration of azithromycin to the eye. '411 patent col.1 ll.8–10. The patent states that prior to the invention, azithromycin was commonly administered orally for the treatment of antibacterial infections, but was not known to be effective when topically administered to the eye. *Id.* at col.1 ll.22–27. Claim 1 of the '411 patent is representative and recites:

> 1. A method of treating an ocular infection, comprising topically administering to an eye of an animal in need of such treatment an ocular infection-treating amount of azithromycin.

The ISV patents disclose various formulations and methods of using topical azithromycin as a gel eyedrop for treating eye infections. Claim 1 of the '113 patent; claim 16 of the '443 patent; and claim 1 of the '893 patent are representative and recite:

> 1. A process for treating an eye, which comprises: topically applying an aqueous polymeric suspension of an azalide antibiotic, wherein said suspension comprises water, 0.01% to 1.0% of an azalide antibiotic, and 0.1 to 10% of a polymeric suspending agent.

'113 patent claim 1;

> 16. A topical ophthalmic composition comprising an aqueous polymeric suspension comprising water, 0.01% to 1.0% of an azalide antibiotic and 0.1 to 10% of a polymeric suspending agent, wherein said topical ophthalmic composition has an osmotic pressure of from 10 to 400 mOsM and wherein said composition does not contain constituents that are physiologically or ophthalmically harmful to the eye.

'443 patent claim 16;

> 1. A composition comprising water, a polymeric suspending agent and an azalide antibiotic, wherein said composition has a pH of about 6.0 to 6.6.

'893 patent claim 1.

B. HISTORY OF THE DISPUTE

Inspire markets a topical azithromycin solution, which is approved by the Food and Drug Administration ("FDA") and is distributed under the name "Azasite®." The FDA's Approved Drug Products with Therapeutic Equivalence Evaluations (commonly known as the "Orange Book") lists all four of the patents-in-suit for Azasite®.

Sandoz filed an Abbreviated New Drug Application ("ANDA") for its generic version of Azasite® seeking approval prior to the expiration of the patents-in-suit. The ANDA included a certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV) (2012) (commonly referred to as a "Paragraph IV certification") stating that the claims of the patents-in-suit were invalid and/or not infringed. Pursuant to § 355(j)(2)(B), Sandoz notified plaintiffs of the Paragraph IV certification. In response, plaintiffs sued Sandoz for infringing dependent claims 3 and 5 of the '411 patent, which depend from claims 1 and 2; dependent claims 6–9 of the '113 patent, which depend from claims 1–3; independent claims 16 and 44 of the '443 patent; and dependent claims 4, 6, 7, 9–12, 30, 36 and 40 of the '893 patent, which depend directly or indirectly from claims 1 or 23 (collectively, the "asserted claims") under 35 U.S.C. § 271(e).

After claim construction, Sandoz stipulated to infringement but contested the validity of the asserted

claims under 35 U.S.C. § 103(a) (2006).[1] *Insite*, 2013 WL 5975015, at *2. Before trial, Sandoz moved to amend the pre-trial order to include as an exhibit the file history of the European counterpart of the '411 patent (the "EPO file history"). The district court denied that motion because it concluded that the late proffer was prejudicial. A bench trial then ensued. The district court ruled that Sandoz had failed to show by clear and convincing evidence that the asserted claims would have been obvious to a person of ordinary skill in the art and, therefore, upheld the validity of all of the patents-in-suit. *Id.* at *49. Sandoz appeals, contending that the district court "misframed" the obviousness inquiry by adopting plaintiffs' characterization of the problem facing a person of ordinary skill in the art at the time of the invention as the development of "improved topical treatments for ocular infections," *id.* at *20, rather than the narrower problem argued by Sandoz of topically administering azithromycin to treat conjunctivitis. Sandoz also appeals the district court's refusal to admit into evidence the late-proffered EPO file history. We have jurisdiction pursuant to 28 U.S.C. § 1295(a)(1).

II. DISCUSSION

A. STANDARD OF REVIEW

"Following a bench trial on the issue of obviousness, we review the court's ultimate legal conclusions de novo and the underlying factual findings for clear error." *Tyco Healthcare Grp. LP v. Ethicon Endo-Surgery, Inc.*, 774

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[1] Pursuant to § 3(n)(1) of the America Invents Act ("AIA"), Pub. L. No. 112–29, amended § 103 applies to patent applications with claims having an effective filing date on or after March 16, 2013. Because the applications for the patents-in-suit were filed before that date, the pre-AIA version of § 103 applies.

F.3d 968, 974 (Fed. Cir. 2014) (citing *Novo Nordisk A/S v. Caraco Pharm. Labs., Ltd.*, 719 F.3d 1346, 1354 (Fed. Cir. 2013)). "A factual finding is clearly erroneous if, despite some supporting evidence, we are left with the definite and firm conviction that a mistake has been made." *Ferring B.V. v. Watson Labs., Inc.-Fla.*, 764 F.3d 1401, 1406 (Fed. Cir. 2014) (citing *United States v. U.S. Gypsum Co.*, 333 U.S. 364, 395 (1948) and *Alza Corp. v. Mylan Labs., Inc.*, 464 F.3d 1286, 1289 (Fed. Cir. 2006)).

"In review of an order denying a motion to amend, a subject [that] is not unique to patent law, we look to the law of the regional circuit court." *Optivus Tech., Inc. v. Ion Beam Applications S.A.*, 469 F.3d 978, 985 (Fed. Cir. 2006) (quoting *Kalman v. Berlyn Corp.*, 914 F.2d 1473, 1480 (Fed. Cir. 1990)). In the Third Circuit, a motion to amend a pretrial order is reviewed for abuse of discretion. *Petree v. Victor Fluid Power, Inc.*, 831 F.2d 1191, 1194 (3d Cir. 1987).

B. OBVIOUSNESS

A patent is invalid "if the differences between the subject matter sought to be patented and the prior art are such that 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) (2006). As patents are "presumed valid," § 282, a defendant bears the burden of proving invalidity by "clear and convincing evidence," *Takeda Pharm. Co. v. Zydus Pharm. USA, Inc.*, 743 F.3d 1359, 1366 (Fed. Cir. 2014) (citing *Microsoft Corp. v. i4i Ltd.*, 131 S. Ct. 2238, 2242 (2011)).

Obviousness is a question of law, based on underlying factual determinations including: "the scope and content of the prior art"; "differences between the prior art and the claims at issue"; "the level of ordinary skill in the pertinent art"; and "[s]uch secondary considerations as commercial success, long felt but unsolved needs, failure

of others, etc." *Graham v. John Deere Co. of Kan. City*, 383 U.S. 1, 17 (1966). "When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007).

1. THE '411 PATENT

a. The Framing of the Obviousness Question

The district court began its obviousness analysis by addressing a dispute between the parties regarding the proper "framing" of the obviousness question. *Insite*, 2013 WL 5975015, at *19. Plaintiffs argued that the proper question to be considered by the court was whether it would have been obvious to a person of ordinary skill in the art at the time of the invention to develop a topical ophthalmic formulation containing azithromycin. Sandoz argued for a narrower question: whether it would have been obvious that topical azithromycin could be used to treat conjunctivitis. The district court agreed with the plaintiffs and found no reason to limit the question to conjunctivitis and to azithromycin. The district court found that there were options beyond just azithromycin that were available to a formulator when considering topical ophthalmic treatments, *id.* at *22, and that persons of ordinary skill in the art would not have developed formulations that only treated conjunctivitis and not corneal infections, given concerns about the spread of conjunctival infections to the cornea. *Id.*

On appeal, Sandoz argues that the district court erred as a matter of law in its framing of the obviousness inquiry. Sandoz contends that in broadly framing the obviousness inquiry, the district court required Sandoz to prove the obviousness of topical treatments of all manner of eye infections and not merely conjunctivitis with azithromycin. Sandoz contends that this amounts to an

error of law contrary to bedrock legal principles that "'[c]laims which are broad enough to read on obvious subject matter are unpatentable even though they also read on nonobvious subject matter.'" *Muniauction, Inc. v. Thomson Corp.*, 532 F.3d 1318, 1328 n.4 (Fed. Cir. 2008) (alteration in original) (quoting *In re Lintner*, 458 F.2d 1013, 1015 (C.C.P.A. 1972)). Sandoz also relies heavily on *Alcon Research, Ltd. v. Apotex Inc.*, in which this court held that courts should "look at any motivation [for combining references, even] beyond that articulated by the patent." 687 F.3d 1362, 1368 (Fed. Cir. 2012).

Plaintiffs respond that identifying the problem faced by a person of skill in the art is a factual question, on which the district court properly ruled. Plaintiffs contend that nothing in the district court's framing of the issue precluded Sandoz from proving that topical treatment of conjunctivitis would have been obvious, but that Sandoz simply failed to carry its burden—a factual issue not a legal question.

The district court did not clearly err in framing the obviousness inquiry as it did, based on its understanding of the problem facing those skilled in the art at the time the invention was made. Moreover, the district court, in framing the question, did not foreclose Sandoz from attempting to prove that the claims would have been obvious based on the treatment of conjunctivitis by the topical administration of azithromycin.

The obviousness inquiry entails consideration of whether a person of ordinary skill in the art "would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and . . . would have had a reasonable expectation of success in doing so." *Proctor & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009) (internal quotation mark omitted) (quoting *Pfizer, Inc. v. Apotex, Inc.*, 490 F.3d 1348, 1361 (Fed. Cir. 2007)); *see also Bayer Schering Pharma*

AG v. Barr Labs, Inc., 575 F.3d 1341, 1347 (Fed. Cir. 2009). "In considering motivation in the obviousness analysis, the problem examined is not the specific problem solved by the invention." *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006). "Defining the problem in terms of its solution reveals improper hindsight in the selection of the prior art relevant to obviousness." *Monarch Knitting Mach. Corp. v. Sulzer Morat GmbH*, 139 F.3d 877, 881 (Fed. Cir. 1998). And, here, the district court recognized that an overly narrow "statement of the problem [can] represent[] a form of prohibited reliance on hindsight, [because] [o]ften the inventive contribution lies in defining the problem in a new revelatory way." *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377 (Fed. Cir. 2012).

Whether a person of ordinary skill in the art would narrow the research focus to lead to the invention depends on the facts. *Alcon* is not to the contrary. *Alcon* merely holds that *if* the prior art would motivate a person of skill in the art to make the claimed invention, even if that was not based on "the same motivation that the patentee had," the patent would have been obvious. 687 F.3d at 1368. But whether the prior art would so motivate a skilled artisan is a question of fact. *Cf. PAR Pharm., Inc. v. TWI Pharm., Inc.*, 773 F.3d 1186, 1196 (Fed. Cir. 2014) ("'The presence or absence of a motivation to combine references in an obviousness determination is a pure question of fact.'" (quoting *Alza Corp. v. Mylan Labs., Inc.*, 464 F.3d 1286, 1289 (Fed. Cir. 2006))).

Here, the district court did not clearly err in finding that the problem faced by one skilled in the art was broader than merely seeking to use azithromycin to treat conjunctivitis. The district court found that azithromycin's characteristics—including that molecules in its class were "known to be bacteriostatic, to have a limited spectrum of activity, and to require multiple doses per day to penetrate tissue," *Insite*, 2013 WL 5975015, at *19—would make it a poor choice for treating ocular infections.

Furthermore, the district court found "the unique balance of log P, molecular weight, solubility, and charge," also made it "not a good candidate." *Id.* The district court also credited the testimony of plaintiffs' expert, Dr. Asbell, that, desirably, effective treatment of conjunctivitis would include penetration of the cornea as well as the conjunctiva because of the potential that a conjunctival infection could spread to the cornea. *Id.* at *7–8. These factual findings provide sufficient support for the district court's framing of the relevant question.

And the district court's framing of the question did not prevent Sandoz from attempting to invalidate the asserted claims, which were not limited to the cure of conjunctivitis, by proving that it would have been obvious to use azithromycin in a topical treatment to cure that one infection. The problem for Sandoz, as we will next address, is that its proofs simply failed to carry the day in satisfying its clear and convincing burden.

b. The Merits of the Obviousness Determination

Sandoz claims that the '411 patent is an obvious modification of Ilotycin®—a topical formulation of erythromycin (an active ingredient similar to azithromycin)—and Zithromax®, an oral azithromycin formulation used to treat conjunctivitis. Sandoz argues that in light of the teachings of the prior art, it would have been obvious to try azithromycin as a topical treatment of bacterial conjunctivitis, with a reasonable expectation of success. It relies on the testimony of Dr. Reed that azithromycin was the "newer iteration" of erythromycin, with remarkably effective properties and contends that it would have been common sense to substitute a new and improved antibiotic for the antibiotic present in Ilotycin®. *Id.* at *14 (quoting the trial testimony of Dr. Reed).

Sandoz also contends that persons of ordinary skill in the art would have been motivated to use azithromycin in a topical treatment given that it was well known, accord-

ing to Sandoz's expert, Dr. Goren, that topical treatments are generally more effective than oral treatments. It also asserts that while oral use of azithromycin worked through a unique process called phagocytosis, that process was not the only process at work in delivering the drug to infected tissue and persons of ordinary skill in the art would not have been deterred from investigating the topical administration of azithromycin. Finally, Sandoz relies on proposals for the topical use of azithromycin in the treatment of trachoma allegedly made at a 1997 World Health Organization meeting that occurred in Geneva (the "Geneva meeting") and contends that the district court was wrong to disregard and discount this evidence.

Plaintiffs counter by arguing that the district court's factual findings were well-supported and not clearly erroneous. They argue that the district court considered all of the potential drug options and correctly concluded that those options would have directed persons of ordinary skill in the art away from the topical administration of azithromycin. They also assert that there is no correlation between oral and topical ophthalmic drug penetration. Finally, they point to Sandoz's expert's contemporaneous failure to use azithromycin topically prior to the '411 invention as evidence of non-obviousness.

The district court concluded that it would not have been obvious to a person of ordinary skill in the art to formulate a topical azithromycin formulation for ophthalmic treatment of any infection as recited in the asserted claims of the '411 patent. The district court thoroughly and properly considered all of the evidence presented and the various arguments raised by the parties in ruling the asserted claims to be not invalid. We agree.

First, the district court did not clearly err in finding that there were "innumerable" options for ophthalmic

treatments, including fluoroquinolones. *Id.* at *22. Fluoroquinolones "were known to be a better option than azithromycin," because they "were bactericidal[,] could act on a broad range of bacteria [and] were known to penetrate ocular tissue." *Id.* at *21, *22. Furthermore, the district court did not clearly err in determining that those of skill in the art would have been concerned that azithromycin might not penetrate ocular tissue based on its high molecular weight, charge and insolubility in water. *Id.* at *22. Even Sandoz's expert, Dr. Reed, admitted that compounds with high molecular weights and charged compounds might not penetrate ocular tissue. *See id.* at *13.

The district court also did not clearly err in crediting Dr. Asbell's testimony that a person of ordinary skill in the art "would not assume that delivering high concentrations of a drug to the eye topically would ensure that the drug would penetrate the ocular tissue simply because the drug was successful when administered systemically." *Id.* at *8. Dr. Asbell's testimony is supported by the fact that oral azithromycin was delivered to the eye at least in part through phagocytosis—a bloodstream dependent process—which would not occur when azithromycin was administered topically. *See id.* at *11, *21.

The district court did not clearly err in discounting the relevance of Ilotycin®, given that there was conflicting expert testimony on whether it had fallen out of favor by 1996. *See id.* at *9–10. The district court also did not clearly err in discounting Dr. Reed's testimony that erythromycin formulations would make azithromycin formulations obvious, given that Dr. Reed's own 1994 patent for topical ophthalmic treatments listed 24 potential antibiotics, including erythromycin, but did not list azithromycin. *See id.* at *18.

For all of the above reasons, this court concludes that Sandoz has not met its clear and convincing burden and

therefore affirms the district court's determination that the asserted claims of the '411 patent are not invalid.

2. THE ISV PATENTS

The ISV patents disclose various formulations and methods of using topical azithromycin as a gel eyedrop for treating eye infections. The claims essentially call for azalide (azithromycin) in a polymeric suspending agent for topical ophthalmic use. The district court concluded that none of the asserted claims of the ISV patents would have been obvious based on its finding that persons of ordinary skill in the art would not have been motivated to use the water-based polymeric solutions of the prior art in an azithromycin formulation because azithromycin was considered insoluble and unstable in water. *See id.* at *47. In addition, it found that were one to make a topical, water-based azithromycin formulation, one of skill in the art would not use polycarbophil, a gelling polymer, but would instead use a colloidal system. *See id.* The district court also found that many of the other limitations present in the claims were separately not obvious. *See id.* at *48. Finally, the district court found that the secondary considerations of unexpected results and long-felt need favored plaintiffs. *Id.* at *49.

On appeal, Sandoz repeats its "framing of the obviousness question" argument and contends that it would have been obvious to use azithromycin to treat conjunctivitis and to formulate that treatment using DuraSite®, a commercial embodiment of Insite's U.S. Patent No. 5,192,535 (the "'535 patent"), which lists a number of active ingredients, including erythromycin. According to Sandoz, it would have been obvious to replace erythromycin with azithromycin. It also contends that the '411 patent itself is prior art to the ISV patents and that

Example 5 of the '411 patent[2] discloses a water-based azithromycin formulation that renders the asserted claims obvious.

Plaintiffs repeat their argument regarding the framing of the obviousness question and contend that the district properly determined that the ISV patents were not obvious. They argue that the '535 patent is too general and lacked sufficient data to motivate a person of skill in the art to combine azithromycin with polycarbophil. They further contend that the expert testimony presented at trial supports the district court's conclusion that the prior art taught away from the use of an aqueous polymer with azithromycin as recited in the asserted claims of the ISV patents. Plaintiffs also argue that Sandoz failed to show that a person of ordinary skill in the art would have been motivated to select a polymeric solution from among the number of choices available or would have had a reasonable expectation of success in making such a selection. Finally, Plaintiffs argue that the district court correctly held the asserted claims of the ISV patents are not invalidated by the '411 patent.

We have already addressed the framing of the obviousness question in connection with our treatment of the '411 patent, *supra* at 7–10. On the merits, we agree with the district court that Sandoz has not clearly and convincingly shown that the asserted claims of the ISV patents would have been obvious. Sandoz relies on the '535 patent, which mentions the possibility that erythromycin could be combined with polycarbophil. The district court found, however, that the '535 patent discloses a "laundry list of active ingredients" and credited the testimony of Dr. Lee that a researcher would focus on the

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[2] The heading for Example 5 is missing in the specification of the '411 patent. Example 5 is described from column 3 line 57 to column 4 line 2.

patent's examples, none of which mention erythromycin. *See Insite*, 2013 WL 5975015, at *37. We see no clear error in the district court's findings. *See* '535 patent col.8 l.64–col.9 l.25 (listing numerous potential active ingredients).

Sandoz argues that the district court's treatment of the '535 patent is inconsistent with *Merck & Co., Inc. v. Biocraft Labs., Inc.*, which held that just because a "patent discloses a multitude of effective combinations does not render any particular formulation less obvious." 874 F.2d 804, 807 (Fed. Cir. 1989). Sandoz overreads *Merck*. In *Merck*, one reference expressly taught the combination of the compounds claimed in the patent. *Id.* Here, by contrast, selecting from the laundry list of potential active ingredients listed in the '535 patent at best teaches that polycarbophil can be combined with erythromycin. The '535 patent does not mention azithromycin. Thus, the skilled artisan would still need to modify that combination by changing erythromycin to azithromycin. Moreover, as noted above, those of skill in the art would have been concerned about azithromycin's solubility and stability in water, so the modification from erythromycin to azithromycin would be even less obvious.

As for the admissibility of the '411 patent as a reference against the ISV patents, we note that the '119 application (which issued as the '411 patent) was filed in 1998, before the earliest priority date of the ISV patents. The '411 patent is assigned to Pfizer, while the ISV patents are assigned to Insite. The patents are not commonly owned or subject to a duty to assign to a common owner. Accordingly, the '411 patent qualifies as prior art to the ISV patents under 35 U.S.C. §§ 102(e) and 103(c) (2006). The significance of the fact that these patents are not commonly owned, despite their being licensed to Inspire and listed in the Orange Book, may not have been fully appreciated by Sandoz's expert, Dr. Reed, who said he was not basing his opinions on any post-1996 refer-

ences. *Insite*, 2013 WL 5975015, at *24. Be that as it may, the district court's ruling that Dr. Reed was precluded from relying on the '411 patent should not preclude Sandoz from relying on the '411 patent itself as a reference, as it was listed by Sandoz in its pre-trial submission. And the district court, anticipating the possibility of appeal, took the precaution of analyzing whether the ISV patents were obvious over the '411 patent. *Id.* It found that even in light of the '411 patent, the claims of the ISV patents were not obvious. *Id.* at *46. We agree. The district court found the water-based examples of the '411 patent to fall far short of satisfying Sandoz's burden and found persuasive the testimony of Drs. Lee and Ahmed that the examples disclosing azithromycin and water-based polymers raised concerns as to stability. The district court also found persuasive the testimony of Drs. Reed and Lee that there were significant differences between Carbopol disclosed in the '411 patent and the polycarbophil of the ISV patents. We find no clear error in the district court's fact-finding or the legal conclusion it drew therefrom on the obviousness question.

Finally, we cannot say that the district court clearly erred in finding that there were meaningful secondary considerations. The district court found that a 60-fold increase in the concentration of azithromycin when dosed topically as opposed to orally was unexpected and also found that Azasite® met a long-felt need. *Insite*, 2013 WL 5975015, at *49, *50. Sandoz argues that some increase in concentration was to be expected. *See* Appellant's Br. at 50. Even if true, Sandoz has not shown that a 60-fold increase was expected. Sandoz also offers nothing to rebut the district court's finding that Azasite® met a long-felt need.

In sum, we find that Sandoz has failed to clearly and convincingly show that the claims of the ISV patents would have been obvious.

3. The Exclusion of the EPO File History

Sandoz sought to introduce into evidence the EPO file history, which allegedly chronicled some of the discussions held at the Geneva meeting. Sandoz did not list this document in its original exhibit list. It only sought to amend the exhibit list after the pretrial conference and after briefing and supplemental briefing on the various motions in limine were complete.

In an oral order, the district court refused to allow Sandoz to introduce the EPO file history into evidence. The district court based its decision on several grounds, remarking that Sandoz's attempt to introduce the evidence was "an eleventh hour proffer"; that it would take plaintiffs "quite a bit of preparation" to deal with these documents; that it was "told" but did not know that European patent law would regard oral presentations and accompanying documentation, even if not widely available, as prior art; and that the file contained attorney arguments and not factual statements. The district court acknowledged that, as parties to the original proceedings, plaintiffs were aware of these documents and that "[s]ome courts might consider th[e] [European proceedings] to be pretty powerful evidence."

Sandoz argues that the district court abused its discretion in precluding it from amending the exhibit list. According to Sandoz, the EPO file history contains factual admissions about the date and content of the Geneva meeting relevant to its obviousness case. Sandoz further contends that there was no finding of bad faith or improper tactics in the filing of its motion to amend and that the prejudice to plaintiffs of allowing this evidence would have been minimal. Plaintiffs counter that the district court's basis for excluding this document was sufficient and did not amount to an abuse of discretion.

Federal Rule of Civil Procedure 16(e) states that a "court may modify the order issued after a final pretrial

conference only to prevent manifest injustice." The Third Circuit considers five *Pennypack* factors in determining whether a district court abused its discretion in excluding evidence:

> (1) "the prejudice or surprise in fact of the party against whom the excluded witnesses would have testified" or the excluded evidence would have been offered; (2) "the ability of that party to cure the prejudice"; (3) the extent to which allowing such witnesses or evidence would "disrupt the orderly and efficient trial of the case or of other cases in the court"; (4) any "bad faith or willfulness in failing to comply with the court's order"; and (5) the importance of the excluded evidence.

ZF Meritor, LLC v. Eaton Corp., 696 F.3d 254, 298 (3d Cir. 2012) (quoting *Pennypack Woods Home Ownership Ass'n*, 559 F.2d 894, 904–05 (3d Cir. 1977)). "The importance of the evidence is often the most significant factor." *Id.* (citing *Sowell v. Butcher & Singer, Inc.*, 926 F.2d 289, 302 (3d Cir. 1991) and *Pennypack*, 559 F.2d at 904). A decision to exclude testimony should be disturbed only if there is "'a definite and firm conviction that the court below committed a clear error of judgment.'" *Id.* at 293 (quoting *In re TMI Litig.*, 193 F.3d 613, 666 (3d Cir. 1999)).

Here, we do not have such a definite and firm conviction for several reasons. We agree with the district court's assessment of the relevant *Pennypack* factors as being either neutral or favoring plaintiffs. The district court had ample basis to find prejudice to the plaintiffs as plaintiffs, on the eve of trial, would have had to prepare arguments explaining the differences between European and United States' patent law and the significance of the statements in the prior proceedings. There is also no indication of how plaintiffs would have been able to cure that prejudice. Thus, the first two factors favor plaintiffs.

The third factor, disruption of trial, is neutral at best. Likewise, the fourth factor, bad faith, is neutral, given the fact that the district court made no finding either way on the question of bad faith. "Making no finding on the question of bad faith (which is what the district court did) is quite different from finding that there was no bad faith." *Konstantopoulos v. Westvaco Corp.*, 112 F.3d 710, 720 n.7 (3d Cir. 1997). As for the fifth factor, relating to the importance of the excluded evidence, the district court was correct to at least question the relevance and probative value of the EPO file history under United States law. The situation here is thus notably different from the facts of *ZF Meritor*, where the exclusion of testimony "clear[ly]" foreclosed plaintiffs' suit, despite the fact that they had won at the liability stage. 696 F.3d at 299. This factor, like the others, does not favor Sandoz.

In view of the totality of evidence, we do not have a definite and firm conviction that the district court abused its discretion and have no reason to disturb the district court's decision to exclude the EPO file history.

III. CONCLUSION

For the foregoing reasons, we affirm the district court's determination that the asserted claims have not been shown to be invalid.

AFFIRMED