United States Court of Appeals for the Federal Circuit

04-1252

SYNTEX (U.S.A.) LLC and ALLERGAN, INC.,

Plaintiffs-Appellees,

v.

APOTEX, INC., APOTEX CORP.,
and NOVEX PHARMA,

Defendants-Appellants.

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Appealed from: United States District Court for the Northern District of California

Judge Martin J. Jenkins

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DECIDED: May 18, 2005

Before CLEVENGER, GAJARSA, and PROST, Circuit Judges.

Opinion for the court filed by Circuit Judge GAJARSA. Concurring opinion filed by Circuit Judge PROST.

GAJARSA, Circuit Judge.

Apotex, Inc., Apotex Corp. and Novex Pharma (collectively "Apotex") appeal from the final judgment of the United States District Court for the Northern District of California, which, after a bench trial, held U.S. Patent No. 5,110,493 (the "'493 patent") owned by Syntex (U.S.A.) LLC not invalid, enforceable, and infringed by Apotex's Abbreviated New Drug Application ("ANDA"). Allergan, Inc., Syntex's distributor, has exclusive rights to manufacture the commercial embodiment of the '493 patent

marketed under the trademark ACULAR.[1] Syntex (U.S.A.) LLC v. Apotex, Inc., No. 01-CV-2214 (January 27, 2004). Because we find the district court committed legal error in establishing certain factual predicates to its non-obviousness determination, we reverse the judgment of validity and remand for further consideration consistent with this opinion.

BACKGROUND

A. The Patents and Prosecution History

The '493 patent, entitled "Ophthalmic NSAID Formulations Containing a Quaternary Ammonium Preservative and a Nonionic Surfactant," claims a formulation for sterile, preserved eye drops to treat eye inflammation such as that caused by conjunctivitis or eye surgery.

The '493 patent teaches combining a nonsteroidal anti-inflammatory drug ("NSAID") such as ketoralac tromethamine ("KT") and a quaternary ammonium preservative such as benzalkonium chloride ("BAC") with a surfactant such as octoxynol 40. The NSAID is the active ingredient for reducing eye inflammation. The quaternary ammonium preservative, in turn, kills any bacteria introduced into the eye during administration of the NSAID. However, quaternary ammonium preservatives, such as BAC, do not always mix well with NSAIDs. Neither ingredient is water soluble, and the two active ingredients may react with each other to form complexes when mixed. These complexes will eventually cause the mixture to look cloudy or lose its antibacterial properties.

[1] Hereinafter, the appellees are collectively referred to as "Syntex." ACULAR is a trademark owned by Syntex, Inc.

The chemical arts often solve this type of mixing problem by using surfactants. A surfactant is a "surface active agent" used to make otherwise insoluble chemicals soluble in water. The '493 patent claims to solve the complex formation problem by adding octoxynol 40, a surfactant, to the KT/BAC mixture.

The '493 patent claims ophthalmic formulations (eye drops) useful for treating eye inflammation, methods of using eye drops to treat eye disease, and preservative systems for use in eye drops. The claims of the '493 patent fall into three categories: claims 1 to 7 are composition claims, claims 8 to 14 are method claims, and claims 15 and 16 recite a "preservative system." Claims 1, 8, and 15 are independent claims, the others are all dependent. Claim 1, the basic embodiment of the compound, provides:

> 1. An ophthalmologically acceptable non-steroidal anti-inflammatory drug formulation, comprising:
>
> an opthalmologically acceptable non-steroidal anti-inflammatory carboxyl group-containing drug in an effective amount for ophthalmic treatment between 0.001% and 10.0% wt/vol;
>
> a quaternary ammonium preservative in an antimicrobially effective amount between 0.0001% and 1.0% wt/vol;
>
> an ethoxylated alkyl phenol that conforms generally to the formula $C_8H_{17}C_6H_4(OCH_2CH_2)_nOH$[2] where n has an average value of 40 in a stabilizing amount between 0.001% and 1.0% wt/vol; and an aqueous vehicle q.s. to 100%.

'493 patent, col. 8, ll. 42-55.

The '493 patent issued from U.S. Patent Application No. 07/624,027 ("the '027 application"), which was filed on December 7, 1990. The '027 application was a continuation of U.S. Patent Application No. 07/096,173 ("the '173 application") filed on

[2] This is the formula for octoxynol 40.

September 11, 1987. The two applications were reviewed by different examiners at the Patent and Trademark Office ("PTO").

Each examiner rejected the application before him as obvious in view of U.S. Patent No. 4,349,563 to Gilbert and U.S. Patent No. 4,559,343 to Han in view of McCutcheon's Emulsifiers and Detergents p.154 (1982) ("McCutcheon's"). U.S. Patent No. 4,454,151 to Waterbury, another patent assigned to Syntex, was listed on the '493 patent as prior art, but was not cited by the examiner in his obviousness rejection. The prior art patents Waterbury, Gilbert, and Han all teach ophthalmic formulations containing NSAIDs, quaternary preservatives, and nonionic surfactants to stabilize the formulation. While Waterbury, Gilbert, and Han do not teach the specific use of octoxynol 40, they do teach using the general class of water-soluble nonionic surfactants as stabilizers. Waterbury and Gilbert teach the use of polysorbate 80.[3] McCutcheon's, a comprehensive directory of emulsifiers and detergents, teach that octoxynol 40 was a known stabilizer. According to both examiners, it was well known in the art that surfactants such as octoxynol 40 have a stabilizing effect on ophthalmic compounds containing NSAIDs.[4] The examiner reviewing the '027 continuation application rejected what has become claim 1 on the grounds that "[t]he mere substitution of one [surfactant] for another . . . is not deemed a patentable distinction in the absence of a showing of some unobvious result."

[3] Polysorbate 80 is sometimes referred to as "tween 80" by the PTO, district court, and the parties. For the purposes of this opinion, all references to tween have been replaced with polysorbate 80.

[4] Consequently, within the context of this art, surfactants are sometimes referred to as stabilizers.

Syntex responded to that rejection by asserting that it had provided acceptable data demonstrating results superior to the formulations disclosed by the Han and Gilbert references. Syntex supported its superior results claim with a declaration from Deborah M. Lidgate ("Lidgate"), one of the named inventors. In the declaration, Lidgate stated that "octoxynol 40, and not octoxynol 3 or octoxynol 5, is suitable to use with benzalkonium chloride to prepare a preservative system for an ophthalmic formulation, or to prepare an ophthalmic formulation, of the present application." In presenting her findings of superior results, Lidgate excluded the additional experimental data that she had developed showing octoxynol 12.5 to be a surfactant capable of stabilizing a KT/BAC formulation.

Following this submission, the examiner allowed the application to issue, stating that Syntex had "overcome the prior art rejections . . . by showing that unexpected results are obtained when one uses [octoxynol 40]. These results are unobvious because one of ordinary skill in the art would not have known that one surfactant would outperform other surfactants." The patent issued on May 5, 1992.

Syntex markets the patented ophthalmic formulation as ACULAR. ACULAR embodies the claims of the '493 patent and has been approved by the Food and Drug Administration ("FDA"). From 1993 to 2001, ACULAR captured a substantial market share for ophthalmic anti-inflammation drugs.

B. The Hatch-Waxman Amendments

The Hatch-Waxman Amendments[5] to the Federal Food, Drug, and Cosmetic Act permit an applicant to file an ANDA with the FDA requesting approval of a bioequivalent ("generic") version of a drug that is already listed by the FDA as approved for safety and effectiveness without having to submit additional safety and efficacy data. See 21 U.S.C. § 355(j)(2)(A). The overall scheme of the Hatch-Waxman Amendments is described in detail in our decisions in Mylan Pharmaceuticals, Inc. v. Thompson, 268 F.3d 1323 (Fed. Cir. 2001) and Andrx Pharmaceuticals, Inc. v. Biovail Corp., 276 F.3d 1368 (Fed. Cir. 2002) and need not be repeated here. For the purposes of this opinion it suffices to know that an ANDA may be filed for drugs currently protected by patents and listed in the FDA's Orange Book. Mylan Pharmaceuticals, Inc., 268 F.3d at 1325-26. In its filing, the applicant must certify either (1) that it will not market its drug prior to the expiration of the relevant patents, or (2) that the relevant patents "are invalid or will not be infringed by the manufacture, use or sale of the new drug for which the ANDA is submitted." 21 U.S.C. § 355(j)(2)(A)(vii)(IV). An ANDA applicant filing its application with the FDA and making a Section IV certification must notify the holder of the patent, who may then bring an action against the applicant for infringement under 35 U.S.C. § 271(e)(2). See 21 U.S.C. §§ 355(j)(2)(B)(i) and (j)(5)(B)(iii). In its notice the applicant must include "a detailed statement of the factual and legal basis [sic] of the opinion of the applicant that the patent is invalid or will not be infringed." 21 U.S.C. § 355(j)(2)(B)(iv). Such a notice can state that the patent is invalid on the basis of

[5] The Hatch-Waxman Amendments were enacted as a part of the Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, codified at 21 U.S.C. §§ 355 and 360cc, and 35 U.S.C. §§ 156, 271, 282.

anticipation, obviousness or non-enforceable for patent misuse or inequitable conduct. Submission of an ANDA is an act of patent infringement if the ANDA seeks approval to manufacture, use, or sell a drug that is claimed in a patent or the use of which is claimed in a patent. 35 U.S.C. § 271(e);[6] Eli Lilly & Co. v. Medtronic, Inc., 496 U.S. 661, 676 (1990) ("The function of [35 U.S.C. § 271(e) is] to define a new (and somewhat artificial) act of infringement for a very limited and technical purpose that relates only to certain drug applications.").

C. The District Court Proceedings

Apotex manufactures generic pharmaceuticals. On April 25, 2001, Apotex notified Syntex that it had filed ANDA 76-109 with the FDA to market a generic version of ACULAR including a Section IV certification. In its notice to Syntex, Apotex stated that it believed the '493 patent to be invalid on the grounds of obviousness and inequitable conduct, and not infringed by Apotex's proposed generic version of ACULAR. On June 6, 2001, Syntex filed suit against Apotex for patent infringement.

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[6] 35 U.S.C. § 271(e) provides in relevant part:

> (2) It shall be an act of infringement to submit-
> (A) an application under section 505(j) of the Federal Food, Drug, and Cosmetic Act or described in section 505(b)(2) of such Act for a drug claimed in a patent or the use of which is claimed in a patent, . . . if the purpose of such submission is to obtain approval under such Act to engage in the commercial manufacture, use, or sale of a drug or veterinary biological product claimed in a patent or the use of which is claimed in a patent before the expiration of such patent.

An ANDA is an application under section 505(j) of the Federal Food, Drug, and Cosmetic Act.

The district court held a Markman hearing and issued a Claim Construction Order. In construing two disputed claim terms[7] of the '493 patent, the district court ruled that the term "in a stabilizing amount" in claim 1 was not a limitation, but merely described the intended results of using octoxynol 40 in an "amount between 0.001% and 1.0% wt/vol." '493 patent, col. 8, line 55. The claim term makes clear that combining the recited ingredients in the claimed weight to volume ratio will stabilize the compound.

Syntex moved for summary judgment of infringement based upon the court's specific claim construction. Apotex did not oppose Syntex's motion. The district court compared the claims of the '493 patent with the drug formulation and uses set forth in Apotex's ANDA 76-109 application and determined that there was no factual dispute. The district court found that the generic version of ACULAR identified in the ANDA 76-109 submission would infringe each claim of the '493 patent, and granted Syntex's motion for partial summary judgment that Apotex had literally infringed each claim of the '493 patent.

After a bench trial on the issues of invalidity and unenforceablity, the district court restated its determination that Apotex's proposed generic version of ACULAR infringed all of the claims of the '493 patent. The district court found that ACULAR is coextensive with the method claims of the '493 patent. The district court also determined that Apotex's proposed generic drug is virtually identical to ACULAR in its composition, preservative system, and intended uses. On the basis of these findings, the district court reiterated that the formulation defined by ANDA 76-109 directly infringed claims 1-

[7] The district court's conclusion that the claim term "antimicrobially effective" is not a claim limitation is not being appealed.

6, 8-13, and 15-16 of the '493 patent. The district court further stated that claims 7 and 14 were infringed under the doctrine of equivalents.[8]

The district court held that the '493 patent was not invalid, rejecting Apotex's invalidity arguments based on obviousness. Moreover, the district court concluded that Syntex had overcome the PTO examiner's obviousness objection by making a showing that the prior art taught away from the use of octoxynol 40 in ophthalmic solutions containing BAC and NSAIDs, and that the use of octoxynol 40 generated unexpected results. The district court also found that the substantial success of ACULAR on the market confirmed that the '493 patent claims were non-obvious. Finally, the district court found no inequitable conduct. The court rejected Apotex's contentions that Syntex had affirmatively misrepresented the unexpected nature of octoxynol 40's ability to stabilize the KT/BAC combination by deliberately withholding test results concerning the ability of octoxynol 12.5 to accomplish the same objectives as the claimed surfactant. The district court found that the test results concerning octoxynol 12.5 were not material, and that Syntex lacked intent to deceive the PTO.

Apotex appeals the district court's claim construction ruling, its judgment of infringement, its non-obviousness determination, and its finding of no inequitable conduct. We have jurisdiction pursuant to 28 U.S.C. § 1295(a)(1).

[8] Claims 7 and 14, the district court observed, specified a sodium chloride concentration of 0.79%. The ANDA formulation contains 0.8% sodium chloride. The court concluded this minor difference would not permit the ANDA formulation to escape infringement under the doctrine of equivalents.

DISCUSSION

A. Standard of Review

This court reviews de novo the grant of summary judgment. Genzyme Corp. v. Transkaryotic Therapies, Inc., 346 F.3d 1094, 1096 (Fed. Cir. 2003). Summary judgment is appropriate when there are no genuine issues of material fact and the moving party is entitled to judgment as a matter of law. Fed. R. Civ. P. 56(c); Anderson v. Liberty Lobby, Inc., 477 U.S. 242, 247-48 (1986). A determination of patent infringement consists of two steps: (1) the court must first interpret the claim, and (2) it must then compare the properly construed claims to the allegedly infringing device. See Cybor Corp. v. FAS Techs., Inc., 138 F.3d 1448, 1454 (Fed. Cir. 1998) (en banc). Claim construction, the first step, is a matter of law that this court reviews de novo. Id. at 1456. Generally, the second step is a factual question that we review for clear error. Bai v. L & L Wings, Inc., 160 F.3d 1350, 1353 (Fed. Cir. 1998). However, factual inferences that are material to the grant of a summary judgment are not accorded such deference—they are reviewed to ascertain whether there is a genuine issue of material fact. Lemelson v. TRW, Inc., 760 F.2d 1254, 1260 (Fed. Cir. 1985).

This court reviews for clear error the district court's determination of the factual inquiries underlying obviousness, while it reviews de novo the legal conclusion that a claim is invalid as obvious. McNeil-PPC, Inc. v. L. Perrigo Co., 337 F.3d 1362, 1368 (Fed. Cir. 2003), cert. denied, 540 U.S. 1107 (2004). The factual determinations relevant to the obviousness inquiry include: (1) the scope and content of the prior art; (2) the differences between the claimed invention and the prior art; (3) the level of ordinary skill in the art; and (4) secondary considerations, if any, such as commercial

success, unexpected results, copying, long-felt but unresolved need, and the failure of others to develop the invention. Graham v. John Deere Co., 282 U.S. 1, 17-18 (1966). "What the prior art teaches, whether it teaches away from the claimed invention, and whether it motivates a combination of teachings from different references are questions of fact." In re Fulton, 391 F.3d 1195, 1199-1200 (Fed. Cir. 2004).

A finding of inequitable conduct is committed to the trial judge's discretion and is reviewed under an abuse of discretion standard. Kingsdown Med. Consultants, Ltd. v. Hollister, Inc., 863 F.2d 867, 876 (Fed. Cir. 1988). "To overturn such a determination, the appellant must establish that the ruling is based on clearly erroneous findings of fact or on a misapplication or misinterpretation of applicable law, or evidences a clear error of judgment on the part of the district court." Molins PLC v. Textron, Inc., 48 F.3d 1172, 1178 (Fed. Cir. 1995) (citing Kingsdown Medical Consultants, 863 F.2d at 876. Findings of materiality and intent are factual findings subject to the clearly erroneous standard and, therefore, will not be disturbed on appeal unless this court has a definite and firm conviction that a mistake has been committed. Id.

B. Claim Construction

Apotex challenges the district court's claim construction on the ground that the term "in a stabilizing amount" should properly be read as a claim limitation. We agree with the district court that the term "in a stabilizing amount" simply describes the intended result of using the weight to volume ratios recited in the claims. Accordingly, we conclude that the district court correctly construed the disputed term of the '493 patent and correctly determined that Apotex's proposed generic version of ACULAR

would infringe all of the claims of the '493 patent. We now turn to Apotex's assertions of invalidity and unenforceability.

C. Obviousness

On appeal, the critical issue is whether the use of the surfactant octoxynol 40 in the claimed formulations is an obvious alteration of similar formulations taught in the prior art. Because the district court clearly erred in its fact findings regarding obviousness, we remand for further consideration.

At trial, Apotex argued that based on the prior art, a person of ordinary skill in the art would expect to succeed in stabilizing a formulation containing an NSAID and BAC with a nonionic surfactant. Contending that the formulation claimed in the '493 patent is just such a formulation, Apotex argued that it is legally obvious.

After conducting a bench trial, the district court made factual findings pertaining to the issue of obviousness. The district court noted that because the prior art at issue had been before the examiner during prosecution, the burden of proving the challenged claims obvious "is particularly high." Syntex (U.S.A.) LLC v. Apotex, Inc., No. 01-CV-2214, slip op. at 40, (Dec. 29, 2003). The trial court then concluded that Apotex had failed to meet this heightened burden. In particular, the court held that nonobviousness was demonstrated by the fact that octoxynol 40 had never been used in a drug formulation; there was no motivation to combine the prior art references, which teach away from the use of the surfactant octoxynol 40; that the use of octoxynol 40 in the claimed formulation produced unexpected results; and that Syntex had provided convincing evidence of the commercial success of ACULAR, the product purportedly covered by claims of the '493 patent. Syntex, slip op. at 45.

Our review of the record reveals clear error by the district court in several of the grounds that led it to conclude that the invention claimed by the claims in suit would not have been obvious. First, the court clearly erred in finding that "[n]o pharmaceutical formulation other than ACULAR has ever included Octoxynol 40." Second, the court clearly erred in discussing the McCutcheon reference and in finding that each of the Waterbury, Gilbert, and Han references teach away from the use of octoxynol 40 in the claimed formulations. Further, the court was under the impression that, in the absence of evidence that those references teach away from combination, there was a failure of proof that there would have been any motivation by one of ordinary skill in the art to use octoxynol 40 in the claimed formulations. In so concluding, the district court failed to examine the expert testimony of Dr. Mitra on the question of whether one of ordinary skill in the art would have deemed the invention obvious, and as a subset of the overall obviousness question, whether octoxynol 40 produced the unexpected results asserted by Syntex. In addition, we think the district court failed to appreciate that the prosecution history of the relevant patents, while not establishing inequitable conduct, casts some doubt on the final examiner's conclusion that the claimed surfactant produces unexpected results sufficient to overcome a prima facie case of obviousness. Finally, we feel the district court should reconsider the significance of the commercial success of the patented formulation in light of our recent decision in Merck & Co. v. Teva Pharmaceuticals. USA, Inc., 395 F.3d 1364 (Fed. Cir. 2005).

On remand, the district court's reconsideration of the obviousness issue should proceed in light of our corrections of the record.

1. Use of Octoxynol 40 in Pharmaceuticals

The district court erred in finding that octoxynol 40 was not used in pharmaceuticals prior to its use in the patented invention. This finding is clearly contradicted by statements in the record made by Lidgate and Fu, inventors of the '493 patent. Lidgate and Fu are both named authors of a Pharmaceutical Report published in September of 1987, that clearly states that octoxynol 40 was a well known ingredient in pharmaceutical products. Although Syntex contends that because this report was published five days after the priority date of the '493 patent it discloses no "prior uses" of octoxynol 40, we think it incredulous that octoxynol 40 could progress from no use, to "well known . . . in pharmaceutical products" in a matter of five days. Accordingly, this report reflects that the use of octoxynol 40 in pharmaceutical compositions was known in the art at the relevant time, an important fact to consider in assessing the obviousness of the claims in suit.

2. Teaching Away

The district court clearly erred in concluding that the Waterbury, Han, and Gilbert references teach away from the use of octoxynol 40 as a nonionic surfactant in ophthalmic formulations involving NSAIDs and BAC. In addition, the district court incorrectly dismissed the relevance of the McCutcheon reference to the overall obviousness analysis. What a reference teaches or suggests must be examined in the context of the knowledge, skill, and reasoning ability of a skilled artisan. What a reference teaches a person of ordinary skill is not, as Syntex's expert appears to believe, limited to what a reference specifically "talks about" or what is specifically "mentioned" or “written” in the reference. Under the proper legal standard, a reference

will teach away when it suggests that the developments flowing from its disclosures are unlikely to produce the objective of the applicant's invention. In re Gurley, 27 F.3d 551, 553 (Fed. Cir. 1994). A statement that a particular combination is not a preferred embodiment does not teach away absent clear discouragement of that combination. In re Fulton, 391 F.3d at 1199-1200.

The trial court found that the Waterbury reference teaches away from the use of octoxynol 40 because the only formulation disclosed in the patent did not include a surfactant, and the only surfactant mentioned in the reference was polysorbate 80. This is error because a prior art reference that does not specifically refer to one element of a combination does not, per se, teach away. If it did, only references that anticipate could be used to support an obviousness analysis. However, prior art references that are capable of rendering an invention obvious under a section 103 analysis are not limited to reference that also anticipate the patent at issue. The trial court's finding that Waterbury teaches away is also error because at col. 13, ll. 44-48, Waterbury discloses "ophthalmic formulations" with "active ingredient . . . stabilizer, and preservative."

The Han reference was deemed to teach away because, although it disclosed the use of NSAIDs, BAC, and nonionic surfactants in ophthalmic formulations, col. 3, Example 1, the nonionic surfactants it mentioned did not include octoxynol 40. This was error, because Han teaches NSAIDs, BAC, and nonionic surfactants. As with the Waterbury reference, the fact that octoxynol 40 was not one of the surfactants mentioned does not, without more, support the contention that the use of octoxynol 40 is nonobvious.

Gilbert, according to the district court, teaches away because it "states explicitly that a stabilizer is not preferred." Syntex, slip op. at 35. This is error because although the preferred embodiment of Gilbert does not use a stabilizer, Gilbert discloses at col. 3, ll. 11-22 ophthalmic formulations that "optionally . . . contain a stabilizer." Gilbert also discloses the combination of an NSAID, BAC, and a surfactant, and discloses a number of stabilizers, of which at least some, according to Apotex's expert Dr. Mitra, are nonionic surfactants.

Finally, the district court discounted the significance of the McCutcheon's reference to the use of octoxynol 40 because although it identified octoxynol 40 as an emulsifier and a stabilizer, it did not describe the use of octoxynol 40 in pharmaceuticals and indicated that it had other uses. McCutcheon's cannot be so lightly overlooked, because, as noted above, the record shows that octoxynol 40 was previously used in pharmaceuticals.

On remand, the district court should reevaluate the importance of these references with the understanding that they provide material disclosure and do not teach away.

3. Apotex's Expert Testimony

The district court, in concluding that the cited references teach away from combination, further found that the evidence produced no motivation to combine. While the question of whether to combine McCutcheon's with other references is a live issue on remand, there is another focus that needs to be appreciated to fully explore the obviousness issue.

As the district court appreciated, the bare question of whether it would have been obvious to substitute one surfactant for another misplaces the proper focus on the obviousness of the invention as a whole, and likely invites hindsight conclusion, forbidden by our precedent. See Gillette Co. v. S.C. Johnson & Son., Inc., 919 F.2d 720, 724-25 (Fed. Cir. 1990).

Apotex's expert testimony, however, cannot be lightly disregarded on the theory that Dr. Mitra only sought to show the obviousness of substituting octoxynol 40 for another surfactant. Mitra's testimony may be relevant on another level, which is the very point on which the examiner concluded that the otherwise suspect invention was non-obvious. Mitra's testimony has to be considered as well on the point of whether the results produced by use of octoxynol 40 are sufficiently unexpected as to secure the validity of the claims in suit.

In this case, Apotex's expert provided his theory of why a person of skill in the art would not have found it unusual to seek, find, and employ octoxynol 40 in making formulations such as those claimed in the '493 patent. Dr. Mitra explained that the references at issue informed a scientist to use water-soluble, micelle-forming,[9] nonionic

[9] A micelle-forming compound has a hydrophilic side (water-loving) and a hydrophobic side (water-hating). When bound together in such a manner that they form a surface, the two sided nature of such compounds enable them to form little bubbles, known as micelles. When the micelle is formed such that the hydrophilic side is on the outside of the bubble and the hydrophobic side is on the inside of the bubble, a sufficiently large micelle can encapsulate hydrophobic compounds inside the bubble. A micelle formed in this manner can enable otherwise insoluble compounds to dissolve in water.

surfactants act as stabilizers in a KT/BAC ophthalmic formulation.[10] He also set forth a scientific rationale for the informed selection of certain nonionic surfactants, and testified that octoxynol 40 was known and used in many products, including cosmetics.[11] Dr. Mitra also opined that knowledge of the chemical qualities of surfactants useful to the claimed subject matter would cause a person, "as a matter of science" to "go into another nonionic surfactant like octoxynols."

To be clear, we do not require that the district court credit all (or any) of this testimony. On remand, however, the district court should consider Apotex's claim of obviousness in light of the applicable legal principles and unencumbered by the factual errors identified above.

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[10] In his Expert Report, Dr. Mitra stated that "[t]he Waterbury '151 patent shows that the non-ionic surfactant polysorbate 80 solubilizes BAC. Therefore, one would expect that other non-ionic surfactants such as octoxynol 40, function as a surfactant." Dr. Mitra also stated that

> [b]y the time of the claimed invention on or before 1987, one of ordinary skill in the art of ophthalmic pharmaceutical formulations would have known that . . . . non-ionic surfactants, such as polysorbate 80, were used in ophthalmic formulations as a surface active agent as a solubilizer, to increase spreading and to reduce surface tension. Octoxynol 40 was known as a non-ionic surfactant as shown by Grant & Hackh's Chemical Dictionary – Fifth Edition, McGraw-Hill, 1987 and GAF product brochures.

[11] Dr. Mitra concluded that "[t]he Waterbury '151 patent shows that the non-ionic surfactant polysorbate 80 solubilizes BAC. Therefore, one would expect that other non-ionic surfactants would work equally well and one would thus look to other patents/publications which show that other non-ionic surfactants such as octoxynol 40, function as a surfactant." Dr. Mitra so concluded because the stabilizer disclosed in Waterbury, polysorbate 80, was a water-soluble, micelle-forming, nonionic surfactant. Dr. Mitra opined that since octoxynol 40 is also a water-soluble, micelle-forming, nonionic surfactant, both compounds are capable of solubilizing the KT/BAC complex by encapsulation.

4. The Prosecution History

The prosecution history makes clear that the PTO initially believed a person of ordinary skill in the art would know to use a nonionic surfactant that possessed the qualities of octoxynol 40 in the claimed formulation. In an Office Action dated April 28, 1989, the examiner rejected claims in the '173 parent application directed to the formulation containing octoxynol 40 because "it is known to use nonionic surfactants." In particular, the examiner stated: "The mere substitution of one nonionic [surfactant] for another, that is, [octoxynol 40] for the nonionic of the primary reference is not deemed a patentable distinction in the absence of some unobvious result."

Syntex responded to this rejection by providing data from a test comparing the efficacy of octoxynol 40, polysorbate 80, and myrj 52, purportedly demonstrating unexpected results. The PTO examiner deemed this showing insufficient:

> It has not been shown that the claimed nonionics provide any unexpected results over the nonionics of the primary references. The data at page 5 of the response shows only that "octoxynol 40" gave somewhat better results than some conventional nonionic surfactants. However, these data do not compare "octoxynol 40" to the nonionics of the primary references. Furthermore the concentrations of the Octoxynol 40 is [sic] greater than that of the other nonionic surfactants. Therefore, no conclusion can be drawn from said data. Also the showing is not commensurate with the claims which, except for claims 8, 9, and 13, recite no proportions and broadly set forth the NSAID, quarternary ammonium preservative and polyoxyethylatedoctylphenol surfactant. Finally, the data (1) do not specify the amount of the NSAID and (2) are not in declaration form. The response therefore does not overcome the rejection.

(Emphases added). The '173 parent application was ultimately abandoned.

The '027 continuation application was assigned to a different PTO examiner. In an Office Action dated February 25, 1991, the new examiner entered the same rejection, restating, verbatim, that: "The mere substitution of one nonionic [surfactant]

for another, that is, [octoxynol 40] for the nonionic of the primary reference is not deemed a patentable distinction in the absence of some unobvious result."

Syntex responded by stating that it had "shown in the prosecution of the parent to this application [the '173 parent application] that other nonionic surfactants, such as [polysorbate 80] and myrj, fail to act as stabilizers in the claimed formulations." This statement contradicted the express finding of the initial PTO examiner that Syntex's earlier data failed to show unexpected results. Whether the second examiner was aware of the earlier rejection of Syntex's claims is unknown. But the relevance of the inconsistency between the views of two examiners is not insignificant.

Syntex supported its view of unexpected results with the Lidgate Declaration, which contained test data purporting to demonstrate the unexpected superiority of octoxynol 40 in comparison to other octoxynols. The applicant's declaration averred that octoxynol 40 is satisfactory for use in the claimed formulation while octoxynols 3 and 5 are unsatisfactory. The Lidgate Declaration, however, omitted data showing that octoxynol 40 did not "outperform other surfactants." The record shows that Syntex knew that, when compared, octoxynol 12.5 and octoxynol 40 produced test samples that "looked equivalent at all temperatures." In addition, the '493 patent itself discussed the use of a shorter chain octoxynol, octoxynol 10, in the disclosed formulations. Although we conclude, later in this opinion, that Syntex did not commit inequitable conduct as charged (notably, Apotex never asserted that Syntex's arguments to the second examiner are suspect), we think the unvarnished view of the prosecution history shows some weakness in the conclusion that the patentee established unexpected results for the claimed surfactant.

While we recognize that an issued patent is entitled to the presumption of validity, 35 U.S.C. § 282, and that a challenger's burden to show invalidity is more difficult to satisfy when prior art references have been presented to the PTO, Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc., 796 F.2d 443, 447 (Fed. Cir. 1986), we think this case is unusual because certain key facts existed that give rise to some doubt as to the strength of the factual proposition that octoxynol 40 indeed produced unexpected results. With full respect for the general propositions that the issued patent is entitled to a presumption of validity, and that the examiners are expected to perform reasonably, see Bausch & Lomb, 796 F.2d at 447 (we assume that the patent examiner has some expertise in interpreting the references and some familiarity with the level of skill in the art), on remand the district court should review the file history as part of its assessment of whether the invention claimed by the claims in suit are nonobvious.

5. Commercial Success

Given the error in its fact finding, the district court should also reevaluate its analysis of the secondary considerations. The district court appeared to rely heavily on the commercial success of ACULAR. As discussed in Merck, the secondary consideration of commercial success exists largely to provide a means for patentees to show in close cases that subject matter that appears obvious is in law unobvious because a high degree of commercial success permits the inference that others have tried and failed to reach a solution. Merck, 395 F.3d at 1376. In Merck, we held that evidence of commercial success resulted in a particularly weak inference because prior art patents prevented others from competing to reach the solution embodied in the claims at issue. 395 F.3d at 1376-77.

Based on the record, we are of the view that the district court should consider the impact of the Merck analysis on this case. Assuming that the active ingredient in the formulation was previously patented, the commercial success of ACULAR may heavily derive from subject matter that does not on the whole contribute to the patentable distinctiveness of these claims. In such a case, the trial court should carefully consider whether the nexus requirement of our law is satisfied. See In re Huang, 100 F.3d 135 (Fed. Cir. 1996).

D. Inequitable Conduct

This court has held that a breach of the duties of candor, good faith, and honesty when prosecuting patent applications constitutes inequitable conduct. Molins PLC, 48 F.3d at 1178. "[I]nequitable conduct during the prosecution of a patent application renders the subsequently issued patent unenforceable." Life Techs., Inc. v. Clontech Lab., Inc., 224 F.3d 1320, 1324 (Fed. Cir. 2000). Affirmative misrepresentations of a material fact coupled with an intent to deceive can constitute inequitable conduct. See Molins, 48 F.3d at 1178. "Materiality and intent to deceive are distinct factual inquiries, and each must be shown by clear and convincing evidence." Life Techs., 224 F.3d at 1324. Prior to March 16, 1992, this court "held that materiality for purposes of an inequitable conduct determination required a showing that 'a reasonable examiner would have considered such [data] important in deciding whether to allow the patent

application.'"[12] Dayco Prods., Inc. v. Total Containment, Inc., 329 F.3d 1358, 1363 (Fed. Cir. 2003). In making the ultimate determination of inequitable conduct, the trial court "must conduct a balancing test between the levels of materiality and intent, with a greater showing of one factor allowing a lesser showing of the other." Id.

Apotex argues that Syntex's submission of the Lidgate Declaration and the test results excluding data on octoxynol 12.5 constituted inequitable conduct. The district court rejected this argument finding the omitted test results lacking in materiality and finding no intent to deceive the PTO. The district court concluded that test results concerning octoxynol 12.5 were not material because (1) the purpose of the declaration was to show that not all octoxynols would work, not that octoxynol 40 was the only octoxynol that would stabilize the formulation; (2) octoxynol 5 was the closest prior art mentioned by the examiner; and (3) the '493 patent disclosed the potential use of octoxynol 10 as a surfactant thereby putting the examiner on notice that octoxynol 40 was not the only possible useful surfactant.

The district court also concluded that Lidgate, Freyberg, and Fu, the inventors of the '493 patent, lacked intent to deceive the PTO. The district court found the testimony of these individuals to be credible. It also found that Apotex failed to establish by clear and convincing evidence that these individuals breached their duty of good faith and candor to the PTO.

[12] The '027 application was filed on December 7, 1990, and the '493 patent issued on May 5, 1992. In 1992, the rule regarding the standard for materiality of disclosures made to the PTO during prosecution changed. Because the PTO issued its notice of allowability regarding the Lidgate Declaration on December 3, 1991, the previous standard was in effect at all relevant points. Consequently, it is not necessary for us to address the import of this change in standard.

Credibility determinations are the type of factual determinations that are best left to the fact finder, the trial court. Apotex points to no evidence that the district court failed to consider Syntex's conduct, but rather asks us to replace the court's credibility determinations with our own. We decline to do so and find no clear error in the district court's finding of no intent to deceive.

The withheld test results showing that octoxynol 12.5 was capable of stabilizing the KT/BAC formulation, while material to Lidgate's statement that octoxynol 40 was generally superior to other octoxynols in stabilizing the KT/BAC formulation, was not sufficiently material to overcome the insufficient showing of intent.

Given that both materiality and intent must be found and that there was no clear error in the district court's finding of intent, the determination of no inequitable conduct is affirmed.

E. Infringement Analysis

Since we reverse the district court's finding that the '493 patent is nonobvious, we do not reach the question of whether Apotex's submission of an ANDA for a generic version of ACULAR constitutes an act of patent infringement under 35 U.S.C. § 271(e).

CONCLUSION

We affirm the district court's determination that there was no inequitable conduct in the prosecution of the '493 patent. We also affirm the district court's claim interpretation. However, because the district court committed clear error in the findings underlying its determination of nonobviousness, we reverse the court's nonobviousness

determination and remand that issue to the district court for further consideration of obviousness. Accordingly, the judgment of the district court is

AFFIRMED-IN-PART, REVERSED-IN-PART AND REMANDED-IN-PART.

COSTS

Each party shall bear its own costs.

United States Court of Appeals for the Federal Circuit

04-1252

SYNTEX (U.S.A.) LLC and ALLERGAN, INC.,

Plaintiffs-Appellees,

v.

APOTEX, INC., APOTEX CORP.,
and NOVEX PHARMA,

Defendants-Appellants.

PROST, Circuit Judge, concurring.

I agree with the majority's well-reasoned analyses with respect to almost all of issues raised in this case, as well as the majority's decision to remand this case to the district court for reconsideration of whether the '493 patent is invalid for obviousness. I write separately only to point out my disagreement with one particular portion of the majority's opinion.

I respectfully disagree with the opinion's focus on the proceedings at the Patent and Trademark Office ("PTO") when analyzing whether the district court correctly found that the claimed ophthalmic formulation produced unexpected results. The majority analyzes the prosecution history of the '493 patent, pointing out an "inconsistency between the views of two examiners" in the parent and continuation applications and a statement during prosecution that the majority believes "contradicted the express finding of the initial PTO examiner." Ante, at 20. In light of these aspects of the prosecution history, the majority concludes that "this case is unusual because key facts existed that

give rise to some doubt as to the strength of the factual proposition that octoxynol 40 indeed produced unexpected results" and instructs the district court to "review the file history as part of its assessment of whether the invention claimed by the claims in suit are nonobvious." Ante, at 21. Thus, the majority requires that the district court analyze the views of separate examiners at the PTO and review statements made by the patent prosecutor for possible mischaracterizations of the prosecution history.

I view this investigation into the prosecution history as problematic in several respects. First, this investigation shifts the focus from the appropriate question for the district court to address on remand: whether the evidence shows the '493 patent claims an ophthalmic formulation that produced unexpected results. Next, as the majority concedes, ante, at 20, Apotex never asserted that Syntex's arguments to the second examiner concerning the prosecution history are suspect. Moreover, had Apotex asserted that these arguments were suspect, I believe the assertion would be relevant to the issue of inequitable conduct and not obviousness. In this regard, I don't view the statement referred to by the majority as a clear mischaracterization of the prosecution history. And the patent prosecutor likely believed the previous data submitted to the first examiner did show unexpected results even if the first examiner believed the data did not. I also find it hard to believe that the second examiner was somehow duped into thinking that the first examiner agreed that the previous data showed unexpected results even if the statement could be understood to be misleading.

In general, I fail to see how the conduct of a patent applicant is relevant to an obviousness determination. Alleged misconduct at the PTO, in terms of either mischaracterizations or omissions, goes to the heart of an inequitable conduct inquiry

but is simply irrelevant to an obviousness inquiry. That is not to say that if evidence showing that a claimed invention does not produce unexpected results was not disclosed to the PTO then that evidence should not be considered by the district court in its obviousness analysis. On the contrary, a district court should consider evidence relevant to an obviousness analysis even if that evidence is not disclosed to the PTO.

In sum, I believe that, here, the district court should address the evidence in the record to determine whether the claimed ophthalmic formulation showed unexpected results. For example, the district court should review all of Lidgate's test results, including test results not disclosed to the PTO such as the comparison of octoxynol 12.5 with octoxynol 40, as well as Dr. Mitra's reasons to discredit some of those test results. In my view, however, there is nothing so unusual about this case as to compel the district court on remand to review alleged misconduct by the patent applicant at the PTO.