407 F.3d 1371 (2005)

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

v.

APOTEX, INC., Apotex Corp., and Novex Pharma, Defendants-Appellants.

No. 04-1252.

United States Court of Appeals, Federal Circuit.

May 18, **2005**.
Rehearing Denied June 13, **2005**.

1372 *1372 *1373 David J. Harth, Heller Ehrman White & McAuliffe LLP, of Madison, Wisconsin, argued for plaintiffs-appellees. With him on the brief were Alexander L. Brainerd, Keith R. Weed, and Olga Rodstein, of Menlo Park, California, and Christine Saunders Haskett, of San Francisco, California.

Manny D. Pokotilow, Caesar, Rivise, Bernstein, Cohen & Pokotilow, LTD., of Philadelphia, Pennsylvania, argued for defendants-appellants. With him on the brief were Robert S. Silver, Alan H. Bernstein, Mona Gupta and William J. Castillo. Of counsel on the brief was Ronald S. Lemieux, Squire, Sanders & Dempsey L.L.P., of Palo Alto, California.

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
1374 preservative, *1374 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.

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 C8H17C6 H4(OCH2CH2)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 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 1375 *1375 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."

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
1376 ANDA applicant *1376 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 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, 110 S.Ct. 2683, 110 L.Ed.2d 605 (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.

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.

1377 *1377 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 16, 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).

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, 106 S.Ct. 2505, 91 L.Ed.2d 202 (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 —
1378 they are reviewed to ascertain whether there is a genuine issue of material *1378 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, 124 S.Ct. 1061, 157 L.Ed.2d 893 (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.,* 383 U.S. 1, 17-18, 86 S.Ct. 684, 15 L.Ed.2d 545 (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
1379 proving the *1379 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

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