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As of: Nov 02, 2015

SYNTEX (U.S.A.) LLC, a Delaware corporation; ALLERGAN, INC., a Delaware corporation, Plaintiffs, v. APOTEX INC., a Canadian corporation; APOTEX CORP., a Delaware corporation; and NOVEX PHARMA, a Canadian corporation. Defendants.

No. C 01-02214 MJJ

UNITED STATES DISTRICT COURT FOR THE NORTHERN DISTRICT OF CALIFORNIA

2006 U.S. Dist. LEXIS 36089

June 2, 2006, Decided
June 2, 2006, Filed

SUBSEQUENT HISTORY: Affirmed by *Syntex (U.S.A.) LLC v. Apotex, Inc., 221 Fed. Appx. 1002, 2007 U.S. App. LEXIS 9276 (Fed. Cir., 2007)*
Related proceeding at *Roche Palo Alto LLC v. Apotex, Inc., 2007 U.S. Dist. LEXIS 67058 (N.D. Cal., Sept. 11, 2007)*

PRIOR HISTORY: *Syntex (USA) LLC v. Apotex Inc., 2006 U.S. Dist. LEXIS 34608 (N.D. Cal., May 18, 2006)*

COUNSEL: [*1] For Syntex USA LLC, a Delaware corporation, Allergan Inc., a Delaware corporation, Plaintiffs: Alexander L. Brainerd, Christine Saunders Haskett, Keith R. Weed, Nathan Shafroth, Heller Ehrman LLP, San Francisco, CA.

For Apotex Inc., a Canada corporation, Apotex Corp., a Delaware corporation, Novex Pharma,

For Defendants: Alan H. Bernstein, Robert S. Silver, William J. Castillo, Caesar Rivise Bernstein Cohen & Pokotilo, Philadelphia, PA; Cameron Kerrigan, Daniel B. Pollack, Squire Sanders & Dempsey LLP, Palo Alto, CA; Ronald S. Lemieux, Paul Hastings Janofsky & Walker LLP, Palo Alto, CA.

For Allergan Inc., a Delaware corporation, Syntex USA LLC, a Delaware corporation, Counter-defendants: Alexander L. Brainerd, Christine Saunders Haskett, Keith R. Weed, Nathan Shafroth, Heller Ehrman LLP, San Francisco, CA.

JUDGES: MARTIN J. JENKINS, UNITED STATES DISTRICT JUDGE.

OPINION BY: MARTIN J. JENKINS

OPINION

FINDINGS OF FACTS AND CONCLUSIONS OF LAW ON RE-HEARING ON ISSUE OF OBVIOUSNESS OF THE 493 PATENT AND PLAINTIFFS' REQUEST FOR PRELIMINARY INJUNCTIVE RELIEF

Pending before the Court is Plaintiffs Syntex (U.S.A.) LLC and Allergan, Inc.'s Request for Preliminary Injunctive Relief. Concurrent [*2] with Plaintiffs' Request, and pursuant to the Federal Circuit's decision in *Syntex (U.S.A.) LLC v. Apotex, Inc., 407 F.3d 1371 (Fed. Cir. 2005)*, is the Court's re-hearing on Defendants Apotex Inc., Apotex Corp., and Novex Pharma's (collectively, "Defendants") obviousness challenge to Plaintiffs' patents-in-suit. In accordance with this Court's Order, the

parties have filed Opening Briefs (Doc. # 469 (Plaintiffs' Corrected Opening Brief "POB"), Doc. # 464 (Defendants' Opening Brief "DOB"), and Responsive Briefs (Doc. # 470 (Plaintiffs' Responsive Brief "PRB"), Doc. # 471 (Defendants' Responsive Brief "DRB"). The Court has carefully considered the parties' arguments as set forth in their briefs and at oral argument, and has thoroughly reviewed and considered the evidentiary record in light of the controlling law and the directives set forth in the Federal Circuit's decision. The Court now rules as follows.

I. Background

Syntex owns *U.S. Patent No. 5,110,493* ("the *493 patent*"), entitled "Ophthalmic NSAID Formulations Containing a Quaternary Ammonium Preservative and a Non-ionic Surfactant." Allergen is the exclusive distributor and manufacturer of formulations [*3] of the *493 patent*, including the product ACULAR(R), an ophthalmic solution used for treating eye inflammation. On April 25, 2001, Defendants notified Plaintiffs pursuant to *21 U.S.C. § 355(j)(2)(B)*, that they had filed Abbreviated New Drug Application ("ANDA") 76-109 with the Food and Drug Administration, wherein Defendants sought approval to market a generic drug version of ACULAR(R). In their notice, Defendants stated that they believed the *493 patent* to be invalid on the grounds of obviousness and inequitable conduct, and not infringed by Defendants' proposed generic version of ACULAR(R).

In response, on June 6, 2001, Plaintiffs filed this lawsuit against Defendants for patent infringement under *21 U.S.C. § 355* and *35 U.S.C. § 271(e)*. Plaintiffs thereafter moved for summary judgment of infringement. The Court granted partial summary judgment for Plaintiffs, finding that the submission of ANDA 76-109 literally infringed each claim of the *493 patent*.

Pursuant to *21 U.S.C. § 355(j)(5)(B)(iii)*, approval of ANDA 76-109 was stayed for 30 months from receipt of Defendants' notification of the [*4] ANDA filing. The stay was set to expire at the end of October, 2003, and, absent a preliminary injunction from this Court, the FDA was then free to approve ANDA 76-109 while the Court's decision on the issue of the *493 patent*'s validity was pending. As a result, on October 17, 2003, Plaintiffs filed a Motion for a Temporary Restraining Order and Preliminary Injunction, requesting that the Court enjoin Defendants from engaging in the commercial manufacture, use, or sale of any product, the approval of which is sought through ANDA 76-109, until the Court determined the validity and enforceability of the *493 patent*.

In ruling on Plaintiffs' Motion, the Court noted that because Plaintiffs had already prevailed on their infringement claim, to prevail on the merits, Plaintiffs only needed to withstand Defendants' invalidity challenges, which included unenforceability due to obviousness, lack of utility, lack of enablement, indefiniteness, and inequitable conduct. Based upon its review of the record, the Court held that Plaintiffs had sufficiently established a substantial likelihood that they would prevail on the issues of patent validity, and that the balance of harms weighed in favor [*5] of granting injunctive relief. The Court therefore granted the preliminary injunction.

In June 2003, in the interim between the Court's ruling on the Motion for Summary Judgment and its Order granting a preliminary injunction, the Court held a bench trial on Defendants' claims of invalidity and unenforceability of the *493 patent*. Subsequently, on December 29, 2003, the Court issued its Findings of Fact and Conclusions of Law ("the December 29 Order"), wherein it concluded that Defendants' proposed generic version of ACULAR(R) directly infringed all of the claims of the *493 patent* and that the *493 patent* was not invalid. In particular, the Court rejected Defendants' invalidity arguments based on obviousness. The Court also affirmed the preliminary injunction by permanently enjoining Defendants from selling products described in ANDA 76-109. Defendants thereafter appealed this Court's determination of non-obviousness to the Court of Appeals for the Federal Circuit.

On May 18, 2005, the Federal Circuit issued its Order reversing this Court's ruling on non-obviousness and outlining criteria that the Court is to consider on remand. Defendants subsequently moved to vacate the permanent [*6] injunction pursuant to *Federal Rule of Civil Procedure 60(b)(5)*. The Court denied Defendants' request; however, on December 15, 2005, the Federal Circuit vacated the permanent injunction. (Doc. # 437.)

Thereafter, on December 16, 2005, Plaintiff filed an Application for a Temporary Restraining Order, seeking to prevent Defendants from commercially manufacturing, using, offering to sell, or selling within the United States or importing into the United States any drug product the approval for which is sought through ANDA 76-109. On December 29, 2005, the Court granted Plaintiffs' Motion for a Temporary Restraining Order (Doc. # 447). The parties subsequently stipulated that the Temporary Restraining Order would remain in effect until the Court's hearing on the Plaintiffs' Motion for a Preliminary Injunction and concurrent hearing on the issue of obviousness. (Docs. # 463, 473.) On February 23, 2006, the Court held a hearing on Plaintiffs' Motion for Preliminary Injunction and on Defendants' obviousness challenge to the claims of the *493 patent* pursuant to the Federal Circuit's remand. The Court now makes the following factual findings and legal [*7] conclusions on the issue of obviousness and Plaintiffs' request for injunctive relief. [1]

1 As an initial matter, also pending before the Court is Plaintiffs' Motion to Remove from the Record Evidence Inadvertently Placed in the Record at Trial (Doc. # 427). In their Motion, Plaintiffs argue that, although the Court only admitted specific pages from Dr. Mitra's expert report during trial, the entire report was placed in the record. (Mot. at 2.) Defendants oppose Plaintiffs' Motion, arguing that granting the Motion would contravene the Federal Circuit's mandate, and that even if the Court only admitted selected pages from the report into evidence, Plaintiffs failed to correct this error. In support of their Motion, Plaintiffs cite the following exchange from trial:

Mr. Silver:	And then, your honor, Dr. Mitra testified about some of
	the charts within and graphs you saw today. He testified
	about figures 3 and 4 on surface tension when Mr. Weed
	asked him questions; there was testimony on other pages
	as well, and those pages of the actual report are: 20, 22,
	23, 24, 25, 31, and 36. And then at the end, 74 through
	78, are just one of two sentences about each of the tables
	that he also testified about. So I would offer those
	particular pages so that the record will be clear,
	because his testimony relied upon it.
Ms. Haskett:	We would object to pages out of the actual report as being
	hearsay.
The Court:	I'll admit them as evidence of the opinion that he has
	given here. I'll admit them.

(R.T. 1891:12-1892:19) (emphasis added). Based on the foregoing except, Defendants only offered, and the Court only admitted (over Plaintiffs' objection), certain pages of Dr. Mitra's report. Accordingly, only pages 20, 22, 23, 24, 25, 31, 36, 74, 75, 76, 77, 78, and exhibits A-N are part of the trial record. The Court therefore **GRANTS** Plaintiffs' Motion to strike all other potions of Dr. Mitra's report from the trial record.

[*8] **II. Obviousness**

A. Findings of Fact

1. Preliminary Factual Findings

1. The *493 patent* issued on May 5, 1992 from Application No. 07/624,027, which was filed on December 7, 1990, and which was a continuation of Application No. 07/096,173, filed on September 11, 1987. The joint inventors of the *493 patent* are Dr. Roger Fu and Deborah Lidgate.

2. There are three types of claims in the *493 patent*: claims to formulations (Claims 1-7), claims to methods of treating disease by using the formulations of Claims 1-7 (Claims 8-14), and claims to a preservative system (Claims 15 and 16). Claims 1, 8, and 15 are the only independent claims in the *493 patent*.

3. Independent Claim 1 claims:

> An ophthalmologically acceptable non-steroidal anti-inflammatory drug formulation, comprising:
>
> > an ophthalmologically acceptable non-steroidal anti-inflammatory carboxyl group-containing drug in an effective amount for ophthalmic treatment be-

tween 0.001% and 10.0% wt/vol;

a quaternary ammonium preservative in an antimicrobially effective amount between 0.001 % and 1.0% wt/vol;

an ethoxylated alkyl phenol that conforms generally to the formula: [*9]

C3H17C6H4(OCH2CH2)nOH 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. [quantity sufficient] to 100%.

(Trial Ex. 1 at SYN0000204, *493 patent* at col. 8, ll 42-55.)

4. Dependent Claim 2 claims the formulation of Claim 1 wherein the quaternary ammonium preservative is benzalkonium chloride ("BAC"); dependent Claim 3 claims the formulation of Claim 2 wherein the ophthalmologically acceptable non-steroidal anti-inflammatory carboxyl group-containing drug is selected from the group selected from ketorolac, indomethacin, flurbiprofen, and suprofen; dependent Claim 4 claims the formulation of Claim 3 wherein the ophthalmologically acceptable non-steroidal anti-inflammatory carboxyl group-containing drug is ketorolac tromethamine; and dependent Claim 5 claims the formulation of Claim 1, further comprising a chelating agent in an amount between 0.01% and 1.0% wt/vol; a tonicifier q.s. to achieve isotonicity with lacrimal fluid; and 1N NaOH or 1N HCl q.s. to adjust pH to 7.40.4. (Trial Ex. 1 at SYN0000204, *493 patent* at col 8, ll 56-68-col. 9, ll 1-10.)

5. Dependent Claims 6 and 7 claim specific compositions [*10] included within Claim 1, wherein the ophthalmologically acceptable non-steroidal anti-inflammatory carboxyl group-containing drug (Claim 6) or ketorolac tromethamine (Claim 7) is present at 0.50% wt/vol; BAC is present at 0.02% wt/vol (of a 50% aqueous solution); Octoxynol 40 is present at 0.01% wt/vol (of a 70% aqueous solution); Na2EDTA is present at 0.10%; NaCl is present either at q.s. for isotonicity with lacrimal fluid (Claim 6) or at 0.79% wt/vol (Claim 7); the pH is adjusted to 7.4"0.4; and purified water is present at q.s. to 100%. Thus, Claims 6 and 7 are more specific than Claims 1-5, requiring formulations of specific ingredients in specific amounts. (Trial Ex. 1 at SYN0000205, *493 patent* at col. 9 at 11-47.)

6. The method of treatment claims of the *493 patent* begin with independent Claim 8. Claim 8 claims "[a] method of treating an ophthalmic disease caused by, associated with, or accompanied by inflammatory processes, comprising administering to a mammal suffering therefrom a formulation comprising" the formulation of Claim 1. (Trial Ex. 1, at SYN0000205, *493 patent* at col. 9, ll 49-64.) Dependent Claims 9-14 claim the method of Claim 8 using the formulations [*11] of Claims 2-7, respectively. (Trial Ex. 1 at SYN0000205, *493 patent* at col. 9, ll65-col. 10, ll 50.) Thus, Claims 13 and 14 claim methods of treating ophthalmic disease by administering the very specifically claimed formulations of Claims 6 and 7.

7. Claims 15 and 16 are the preservative system claims. Independent Claim 15 claims "[a]n antimicrobially effective preservative system for an ophthalmologically acceptable non-steroidal anti-inflammatory carboxyl group-containing drug formulation, comprising: a quaternary ammonium preservative in an antimicrobially effective amount between 0.001% and 1.0% wt/vol of the formulation; and [Octoxynol 40] in a stabilizing amount between 0.001% and 1.0% wt/vol of the formulation." Dependent Claim 16 claims the preservative system of Claim 15 wherein the preservative is BAC. (Trial Ex. 1, at SYN0000205, *493 patent* at col. 10, ll 52-65.)

8. An Information Disclosure Statement ("IDS") was filed along with both applications, identifying the following prior art: 4,087,539 (1978) Muchowski *et al.*; 4,089,969 (1978) Muchowski *et al.*; 4,097,579 (1978) Muchowski *et al.*; 4,232,038 (1980) Kluge *et al.*; 4,336,151 (1982) Like [*12] *et al.*; 4,336,152 (1982) Like *et al.*; 4,545,151 (1984) Waterbury; "Influence of (Ethoxy)5 Octyl Phenol on the Antibacterial Properties of Preservatives," M.T. Nadir, *et al., Journal of Pharmacy and Pharmacology*, Volume 29, Supplement, December 1977, page 67P; and "Ocufen (flurbiprofen sodium) 0.03% Liquifilm sterile ophthalmic solution, Allergan, product description sheet.

9. In addition, the examiner cited the following references in initially rejecting certain claims of the *493 patent* under *35 U.S.C. § 103*: 4,087,538 (1978) Portnoff; 4,230,724 (1980) Cooper *et al.*; 4,474,751 (1984) Haslam *et al.*; 4,474,811 (1984) Masuda *et al.*; 4,500,538 (1985) Woltersdorf; 4,559,343 (1985) *Han et al.*; 4,607,038 (1986) Ogata *et al.*; Japanese Ref. No. 23,318 (1985); 4,349,563 (1982) Gilbert *et al.; The Condensed Chemical Dictionary*, Seventh Ed.; *McCutcheon's "Emulsifiers and Detergents"* (1982) ("*McCutcheon's*");

"The Synergistic Effects of Nonionic Surfactants Upon Cationic Germicidal Agents," Schmolka (1973). (Trial Exs. 024 at SYN0000245-48, 035 at SYN0000034-44, SYN0000050-52.)

10. A person of ordinary skill in the art [*13] at the time of the invention is a person having a Bachelor's or Master's degree in the pharmaceutical sciences and having three to five years of experience working in the field under the supervision of a person having a Ph.D. in the pharmaceutical sciences. (R.T. 1707:11-24; DOB at 5 n.3.)

2. The Prior Art References

11. Plaintiffs assert that at trial, Defendants only asserted that the combination of *U.S. Patent No. 4,545,151* to Waterbury, *U.S. Patent No. 4,349,563* to Gilbert *et al.*, and *U.S. Patent No. 4,559,343* to Han *et al.*, rendered obvious the claims of the *493 patent*. Defendants, however, contend that in addition to these references, they also relied on: (1) *McCutcheon's*; (2) the Pharmaceutical Expert Report; (3) *Grant and Hackh's Chemical Dictionary*; (4) the GAF product sheet; (5) the Cosmetic Dictionary; (6) the Nadir reference (Trial Ex. YK); (7) the Schmolka reference; and (8) the Condensed Chemical Dictionary. Plaintiff does not dispute that each of the references that Defendants cited are in the trial record. Because the inclusion of the additional references cited by Defendants does not affect the Court's ultimate determination on the issue [*14] of obviousness, the Court will consider all the references that Defendants have cited. However, based on its review of the trial record, the Court finds that Defendants' obviousness challenge relied primarily on the Waterbury patent, the Gilbert patent, the Han patent, and *McCutcheon*'s.

12. *U.S. Patent No. 4,454,151* to Waterbury (the "*151 patent*" and/or the "Waterbury patent") defines a number of non-steroidal anti-inflammatory drugs that were found to be efficacious in the treatment of inflammatory diseases.

13. The Waterbury patent does not discuss the concepts of long-term stability or anti-microbial effectiveness and does not discuss any problem of interaction or complexation between BAC and ketorolac tromethamine. It also does not discuss the use of EDTA or any other chelating agent. (Trial Ex. 004; R.T. 1158:1-16, 1159:2511 60:3, 1707:25-1710:6.)

14. Although the only example formulation in the Waterbury patent, Example 1 ("Composition of Ophthalmic Solutions for Topical Administration to the Eye"), does not include a surfactant in its composition, the Waterbury patent does disclose the use of the surfactant Polysorbate 80 (also referred to as "Tween 80"). [*15] The Waterbury patent, however, discloses Polysorbate 80 as a member in a list of stabilizers -- not surfactants. (Trial Ex. 004 at 13:44-48, 56-57.) The only other stabilizer disclosed in that list is glycerin, which is not a surfactant. (R.T. 1709:5-10.)

15. *U.S. Patent No. 4,349,563* to Gilbert (the "*'563 patent*" and/or the "Gilbert patent") teaches the topical administration to the eye of non-steroidal anti-inflammatory agents, which as a class previously were thought to be ineffective in treating ocular inflammation. The Gilbert patent teaches that NSAIDs for ocular administration should include various ingredients other than the non-steroidal anti-inflammatory agent itself, such as antimicrobial agents, antioxidants, and metal ion sequestering agents. The Gilbert patent does not, however, mention ketorolac tromethamine. (Trial Ex. WJ.)

16. Although the Gilbert patent states that "the presence of a stabilizer is not preferred," the patent does teach the optional inclusion of Tween or Pluronic surfactants, and specifies Polysorbate 80. The Gilbert patent does not mention Octoxynol 40, and does not discuss the concepts of long-term stability or anti-microbial effectiveness [*16] or any problem of interaction or complexation between BAC and NSAIDs. (R.T. 1711:20-1712:7.) It also does not discuss the use of EDTA or any other chelating agent. (Trial Ex. WJ.)

17. *U.S. Patent No. 4,559,343* to Han, *et al.* (the "*'343 patent*" and/or the "Han patent") discloses that the addition of xanthines, such as caffeine, to ophthalmic solutions of acidic NSAIDs helps to reduce the irritation associated with the NSAIDs. (Trail Ex. AK.) Specifically, the Han patent claims an aqueous, nonirritating, non-steroidal ophthalmic composition comprising the NSAID suprofen, a xanthine, a preservative, and a buffer, as well as methods for using this composition. (*Id.*) Two of the examples of the Han patent disclose the use of NSAIDs with either BAC or thimerosal and either Pluronic F127 or tyloxapol, but do not indicate whether Pluronic F127 or tyloxapol are being used as stabilizers, or indicate what role these surfactants play in the example compositions at all. (*Id.*) The Han patent does not discuss the concepts of long-term stability or anti-microbial effectiveness and does not discuss any problem of interaction or complexation between BAC and ketorolac tromethamine. It [*17] also does not discuss the use of EDTA or any other chelating agent. (*Id.*)

18. *McCutcheon's* is a compendium of a large number of emulsifiers and detergents. (Trial Ex. AL.) It describes Igepal CA-897 (Octoxynol 40) as an "Emulsifier, stabilizer." However, *McCutcheon's* does not disclose the use of Octoxynol 40 in a pharmaceutical. (*Id.*) There is nothing in *McCutcheon's* that suggests that Octoxynol 40 could successfully be used to solve the interaction between a carboxyl-group-containing NSAID and a qua-

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