Positive
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-

ternary ammonium preservative. There is nothing in *McCutcheon's* that suggests that Octoxynol 40 could safely be used in a pharmaceutical product or in an ophthalmic formulation. There is nothing in *McCutcheon's* that suggests that the use of Octoxynol 40 would preserve the anti-microbial effectiveness of a preservative.

19. None of the prior art references cited by Defendants disclose any functional equivalence between Octoxynol 40 and any of the surfactants disclosed by the Waterbury, Gilbert or Han patents.

20. Apart from the September 1987 Pharmaceutical Report authored by Dr. Fu and Ms. Lidgate ("the Syntex Report"), none of the prior art references [*18] cited by Defendants mention Octoxynol 40, except for *McCutcheon's*. Defendants' expert, Dr. Mitra, provided no testimony at all regarding *McCutcheon's*.

21. Plaintiffs' expert, Dr. Stella, testified that although *McCutcheon's* refers to Octoxynol 40 as an emulsifier/stabilizer, it uses those words in the context of mixing and stabilizing a non-water-miscible substance and water. This is an entirely different context from the use of those words in the *493 patent*, which discloses the use of Octoxynol 40 as a stabilizer in a solution consisting of an NSAID and a quaternary ammonium preservative. (R.T. 1714:11-19; Trial Ex. 1, claim 1.)

22. Dr. Stella also testified that there was nothing in *McCutcheon's* that would have motivated one of ordinary skill in the art to combine it with the other prior art references to arrive at the patented inventions. (R.T. 1715:17-22.)

23. Significantly, Defendants have not identified any prior art reference that either discloses or suggests: (a) that Octoxynol 40 be used in an ophthalmic formulation; (b) that it be used in a preservative system with a quaternary ammonium preservative; (c) that it be used in a formulation with [*19] a quaternary ammonium preservative, such as BAC; (d) that it be used in a formulation with a carboxyl group-containing NSAID, such as ketorolac tromethamine; (e) that it be used to prevent the formation of a complex between a carboxyl group-containing NSAID and a quaternary ammonium preservative; or (f) that it would act to maintain the anti-microbial effectiveness of a quaternary ammonium preservative, such as BAC, in an ophthalmic formulation.

3. The Prosecution History of the 493 Patent

24. As previously indicated, an IDS was filed along with both Application No. 07/096,173 and Application No. 07/624,027, which led to the issuance of the *493 patent*, 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 *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% [*20] Liquifilm sterile ophthalmic solution, Allergan, product description sheet.

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

26. The results of Ms. Lidgate's study of formulations containing ketorolac tromethamine, BAC, and three different surfactants-Octoxynol 40, Tween 80, and Myrj 52-were also disclosed to the Examiner during the examination of the parent Application No. 07/096,173. These results showed that solutions containing Octoxynol 40 remained clear under a variety of storage conditions [*21] while solutions containing Tween 80 and Myrj 52 became turbid. (Trial Exs. 204, 205, 009, 024 at SYN0000280, 035 at SYN0000057-64; RT. 695:1-701:14, 761:2-762:9, 769:11-770:25.)

27. The examiner of Application No. 07/096,173 criticized the data comparing Octoxynol 40, Tween 80, and Myrj 52 for four reasons: (1) the data did not compare Octoxynol 40 to the surfactants of the primary references; (2) the concentration of Octoxynol 40 was greater than the concentrations of the other surfactants; (3) the data was not commensurate with the then-pending claims, which did not set proportions for the components of the formulations; and (4) the data was not in declaration form. (Trial Ex. 24 at SYN0000288.)

28. The examiner's criticism number (1), that the surfactants of the primary references were overlooked, is no longer relevant at this stage in the proceedings. The data before the examiner compared Octoxynol 40 to the surfactant most mentioned in the primary references-Tween 80. Furthermore, the Court-unlike the examiner-also has before it evidence that Ms. Pulsipher tried to use the Pluronic F127 of Han, as well as Pluronic F168, to solve the ketorolac tromethamine/BAC turbidity [*22] problem, and found that these surfactants were

unable to do what Octoxynol 40 later was discovered to do-namely, keep a solution of ketorolac tromethamine and BAC stable under variable conditions. (R.T. 350:5-375:15.)

29. The examiner's criticism number (2), regarding the relative concentrations of the surfactants used in the experiments was that, whereas the concentrations of Octoxynol 40 are listed as 0.004% and 0.02%, the concentrations of the other surfactants are listed as 0.0035% and 0.01% for Tween 80 and 0.0015% and 0.01% for Myrj 52. Therefore, the "high" and "low" concentrations of Octoxynol 40 are higher, respectively, than the "high" and "low" concentrations of the other surfactants. However, comparing the results for the "low" concentration of Octoxynol 40 (the 0.004% column) with the "high" concentrations of Tween 80 and Myrj 52 (the two columns labeled 0.01%), indicates that Octoxynol 40 still outperforms the other surfactants. In other words, taking, for example, the observations made after one month at 40 [degree] C, a concentration of 0.004% of Octoxynol 40 was able to keep the solution clear, whereas 0.01% concentrations of Tween 80 and Myrj 52-that is, concentrations [*23] two and a half times higher than the Octoxynol 40 concentration-resulted in solutions that were "very turbid" and "turbid," respectively. (Trial Ex. 24 at SYN0000280.)

30. The examiner's criticism number (3), regarding the then-pending claims, is irrelevant at this stage in the proceedings. Unlike the claims that were pending at the time of the examiner's comments, the claims of the *493 patent*, as finally issued and as asserted in this lawsuit, do set forth proportions of the formulation components. (*See* Trial Ex. 001.)

31. Similarly, the examiner's criticism number (4), that the data from Ms. Lidgate's tests was not in declaration form was specific to the prosecution context. The results of Ms. Lidgate's tests, supported by sworn trial testimony from Ms. Lidgate, are in the trial record. Ms. Lidgate's test data compares the performance of Octoxynol 40 with the performance of other micelle-forming, non-ionic surfactants, which Dr. Mitra says should all perform "equally well" and which Defendants have asserted to be the closest prior art to the *493 patent*.

32. Defendants have argued that the data comparing Octoxynol 40, Tween 80, and Myrj 52 should be disregarded [*24] because it contains inconsistencies. Defendants base this argument on the fact that the data shows that all solutions were clear at 60 [degree] C, both at 1 month and at 5 months, thus showing that the turbidity of those particular solutions did not increase with time. Defendants have also pointed to the fact that the Tween 80 solutions at 40 [degree] C were described as "very turbid" at 1 month, but only "turbid" at 5 months, indicating that turbidity may have decreased over time. However, Defendants fail to take into account that all of the solutions containing Octoxynol 40 remained clear, at all temperatures and over all time periods, while the solutions containing Tween 80 and Myrj 52 became turbid under several different time and temperature conditions. (Trial Ex. 24 at SYN0000280.) This demonstrates that the solutions containing Octoxynol 40 had better "robust" stability under a variety of conditions than did the solutions containing Tween 80 and Myrj 52.

33. Defendants have also argued that because the original claims of Application No. 07/096,173 claimed "a stabilizing amount of a nonionic surfactant," Trial Ex. 24 at SYN0000235, the applicants admitted to the PTO [*25] that all nonionic surfactants are the same. The applicants, however, made no such admission and in fact subsequently narrowed the claims to just the use of Octoxynol 40. The prosecution history in its entirety, therefore, supports a conclusion that the applicants did not believe all nonionic surfactants to be the same.

34. Defendants also point to the applicants' statement in the prosecution history that "such compounds [non-ionic polyoxyethylated octylphenol surfactants] are generally known to those skilled in the art as useful surfactant compounds." (Trial Ex. 24 at SYN0000259.) However, the fact that such compounds may have been known to be "useful surfactant compounds," does not support the inference that they were known, prior to the inventions of the *493 patent*, to be useful in ophthalmic formulations or in solubilizing NSAID/BAC complexes. In fact, several other types of known surfactant compounds were specifically found by the Syntex scientists not to be useful in ketorolac tromethamine/BAC formulations.

35. On March 5, 1991, the PTO issued a rejection of all of the claims of Application No. 07/624,027 as obvious over the prior art. The Examiner noted that the [*26] Gilbert and Han patents both taught the use of "nonionic surfactants" as stabilizing agents and stated that any non-ionic surfactant would lead to "better solubilization of said quaternary ammonium compound." (Trial Ex. 35 at SYN0000048.) 36. The examiner of Application No. 07/624,027 also specifically rejected claims 37 and 38 as obvious over the Nadir and Schmolka references. The Nadir reference suggested the use of Octoxynol 5 in conjunction with antibacterial preservatives. (Trial Ex. 035 at SYN0000048, SYN0000090; RT. 766:3-768:22, 771:1-772:4.)

37. In response to the March 5, 1991 rejection, on September 5, 1991, Dr. Derek Freyberg, in-house counsel for Syntex submitted an Amendment of the claims. Specifically, in response to the Examiner's rejection of

claims 37 and 38 over the Nadir reference, Dr. Freyberg submitted a declaration of Ms. Lidgate (the "Lidgate Declaration"). The Lidgate Declaration included the results of a test performed by Ms. Lidgate that compared formulations containing Octoxynol 40, Octoxynol 5, and Octoxynol 3. (Trial Ex. 035 at SYN0000057-64; R.T. 769:11-770:25.)

38. The September 5, 1991 Amendment also stated as follows:

> Applicants [*27] have shown in the prosecution of the parent to this application that other nonionic surfactants, such as Tween and Myrj, fail to act as stabilizers in the claimed formulations; and the enclosed Declaration of Deborah M. Lidgate demonstrates that certain octoxynols are unsatisfactory.

Thus, the Amendment attempted to convince the Examiner that he was wrong in treating all nonionic surfactants alike because at least some surfactants, including certain octoxynols, would not work to stabilize the claimed formulations. (Trial Ex: 035 at SYN0000062.)

39. When Ms. Lidgate turned her data from the experiment in question over to Syntex's patent department, the data included the results of experiments on formulations containing Octoxynol 40, Octoxynol 5, Octoxynol 3, and Octoxynol 12.5. Included in those results was Ms. Lidgate's observation that, after three months of stability testing, the formulations containing Octoxynol 40 and Octoxynol 12.5 looked equivalent. (R.T. 658:1-660:23.)

40. Although Ms. Lidgate noted that the formulations containing Octoxynol 40 and Octoxynol 12.5 looked equivalent, she did not conclude that they were equivalent in any other respect. In particular, [*28] Ms. Lidgate had no evidence that the formulation containing Octoxynol 12.5 would pass the "USP challenge" test for antibacterial effectiveness. (R.T. 651:13-652:12, 660:16-661:8.)

41. While Ms. Lidgate did not make the decision as to which of the octoxynols would be included in the Lidgate Declaration, she believed the Declaration to be accurate and truthful at the time that she signed it. Ms. Lidgate testified that she had no reservations about the fact that the Declaration did not mention Octoxynol 12.5 because the purpose of the Declaration was to show that not all octoxynols would be suitable for use in the patented formulation. (RT. 661:9662:6.)

42. Dr. Freyberg did not include any reference to Octoxynol 12.5 in the Lidgate Declaration because the purpose of the Declaration was to compare the invention with the prior art cited by the examiner-that is, Octoxynol 5. The examiner cited no prior art reference that described an ophthalmic formulation using Octoxynol 12.5, and there is no evidence in the record of the existence of any such prior art reference. (RT. 772:5-774:13.)

43. The examiner mailed a notice of allowance of all claims on December 3, 1991. (Trial Ex. [*29] 131 at SYN0000066.) The *493 patent* issued on May 5, 1992.

4. Use of Octoxynol 40 in Pharmaceuticals

44. In its December 29 Order, the Court found that "[n]o pharmaceutical formulation other than ACULAR(R) has ever included Octoxynol 40." (Doc. # 350 at 126.) In its opinion remanding the case to this Court, the Federal Circuit directed the Court to reconsider that finding in light of the Syntex report. *Syntex, 407 F.3d at 1379.*

45. The Syntex Report states that Octoxynol 40 was a well known ingredient in pharmaceutical products. (Trial Ex. 303 at SYN11264.) At trial, however, Ms. Lidgate could not recall the basis for this statement in the Syntex Report. (R.T. 580:4-21.) Likewise, Dr. Fu testified that he had no knowledge of the statement in the Report. (R.T. 830:15-21.) There was no evidence as to what products the Syntex Report referred to.

46. Additionally, other evidence on the issue contradicted the statement from the Syntex Report. Specifically, Defendants' expert, Dr. Mitra, testified that, prior to its use in ACULAR(R), Octoxynol 40 was never used in a pharmaceutical formulation. (R.T. 1165:3-14.) Dr. Mitra also testified that Octoxynol [*30] 40 was not used in any pharmaceutical product on the market currently except for ACULAR(R). (*Id.*) Octoxynol 40 is not listed in the 1986 Handbook of Pharmaceutical Excipients. (R.T. 1229:7-13.) Thus, no evidence corroborates the statement in the Syntex Report concerning Octoxynol 40, and significant evidence contradicts the statement.

47. Defendants argue that three additional references demonstrate that Octoxynol 40 was "well known in the art." Specifically, Defendants argued that "Grant & Hackh's Chemical Dictionary, the GAF product sheet and the Cosmetic Dictionary all show that O40 was well known in the art." (DRP at 8.) Defendants further argued that "Syntex admitted that [these references] all show that O40 was well known in the art" during prosecution. (*Id.*)

48. Contrary to Defendants' characterization, the applicants did not admit during prosecution that these three references show that Octoxynol 40 was well known in the art. The examiner initially rejected the claims for lack of a written description because "[t]he specification does not adequately define the term Octoxynol 40." (Trial Ex. 24 at SYN0000268.) In response, the applicants cited to

Grant [*31] & Hackh's Chemical Dictionary and to the GAF product sheet, not as prior art, but as evidence that in reading the issued patent, one skilled in the art would recognize Octoxynol 40 as a surfactant compound having a particular chemical formulation. (Trial Ex. 24 at SYN0000276-77; Trial Ex. 35 at SYN000033.) The applicants cited to the "Cosmetic Ingredients Dictionary" merely to inform the examiner that "'octoxynol 40' is not a trademark." (Trial Ex. 35 at SYN000033.) The applicants did not state that these references show that Octoxynol 40 was well known in pharmaceutical formulations or, in particular, as a stabilizer in an NSAID and BAC formulation. (*Id.*) In fact, it has not been shown that any of these references are even from the field of pharmacology.

49. Based on the evidence presented, the Court finds that Octoxynol 40 may have been used in one or more unknown "pharmaceutical products" prior to the time the *493 patent* application was filed. This fact is accorded only limited weight, however, because there was no evidence suggesting what these "pharmaceutical products" might have been or what the particular use of Octoxynol 40 in those products might have suggested to [*32] one of ordinary skill in the art. Moreover, the Court finds that there is no evidence that Octoxynol 40 was used in an ophthalmic product or formulation before the inventions of the *493 patent*.

5. Unexpected Results

50. In its December 29 Order, the Court concluded that the patented inventions produced unexpected results. (Doc. # 350 at 153.) In its opinion remanding the case to this Court, the Federal Circuit directed this Court to reconsider that finding in light of the prosecution history and the testimony of Dr. Mitra. *Syntex, 407 F.3d at 1382-83*. In particular, the Federal Circuit directed this Court to reevaluate the criticisms by the first examiner of the data comparing Octoxynol 40, Tween 80, and Myrj 52, and to reconsider the fact that, during prosecution, the applicants did not submit Ms. Lidgate's results showing that "octoxynol 12.5 and octoxynol 40 produced test samples that looked equivalent at all temperatures.'" *Id., 407 F.3d at 1382-83*. The Federal Circuit also instructed this Court to consider Dr. Mitra's testimony regarding the substitutability of various surfactants in connection with the unexpected results inquiry. [*33] *Id. at 1380-82*

51. As indicated above, the examiner of Application No. 07/096,173 criticized the data comparing Octoxynol 40, Tween 80, and Myrj 52 for four reasons: (1) the data did not compare Octoxynol 40 to the surfactants of the primary references; (2) the concentration of Octoxynol 40 was greater than the concentrations of the other surfactants; (3) the data was not commensurate with the then-pending claims, which did not set proportions for the components of the formulations; and (4) the data was not in declaration form. (Trial Ex. 24 at SYN0000288.)

52. The data in the prosecution history showing that Octoxynol 40 outperformed Tween 80 and Myrj 52 is persuasive on the issue of unexpected results and is not rendered less so by any of the criticisms on the part of the examiner of the 07/096,173 application.

53. The Court has also considered Ms. Lidgate's test results regarding Octoxynol 12.5 and concludes that they do not undermine a finding that the patented inventions produced unexpected results.

54. As previously indicated, although Ms. Lidgate concluded that formulations containing Octoxynol 40 and Octoxynol 12.5 were equivalent from [*34] a visual perspective, she did not determine that they were equivalent in any other respect. Particularly, the testing that Ms. Lidgate performed did not provide data regarding the stability of Octoxynol 12.5 or that it would have been antimicrobially effective. (R.T. 652:7-12; 661:4-5.)

55. Further, even if Octoxynol 12.5 was found to perform as well in the patented formulations as Octoxynol 40 -- an assumption that cannot be confirmed due to the absence of antimicrobial data regarding Octoxynol 12.5 -- this would not detract from the unexpected results demonstrated by the data comparing Octoxynol 40, Tween 80, and Myrj 52. Particularly, it would still be unexpected to find that Octoxynol 40 outperformed these other well-known surfactants, which were disclosed in the prior art references, even if some other surfactants, such as Octoxynol 12.5, were capable of doing the same.

56. Defendants have argued that Ms. Lidgate's experiments that led to the submission of the Lidgate Declaration improperly lacked a "control formulation" -- that is, a formulation to which other formulations are compared. In fact, the formulation containing Octoxynol 40 was the formulation that other [*35] formulations were being compared against, and it therefore acted as the "control" formulation in the experiments. (R.T. 621:6-622:17.)

57. Dr. Mitra's testimony that a surfactant's micelle-forming and non-ionic properties would necessarily enable that surfactant to have stabilizing abilities, and that therefore it was to be expected that Octoxynol 40 would function "equally [as] well" as other micelle-forming, non-ionic surfactants in stabilizing ophthalmic formulations, (R.T. at 1016:1-1018:15; *id.* at 1054:6-24; *id.* at 1122:14-1123:13; *id.* at 1129:3-16), fails on two levels to support a finding that Octoxynol 40's performance was not expected. First, if the state of knowledge at the time the inventions was that all mi-

celle-forming, non-ionic surfactants would work "equally well," then Plaintiffs' evidence of the results of testing carried out by Ms. Lidgate -- showing that Octoxynol 40 outperformed two other much more well-known micelle-forming, non-ionic surfactants -- is highly unexpected. (R.T. 695:1-701:14; Trial Exs. 204 & 205.) Moreover, the corollary to Dr. Mitra's substitutability theory, namely that Octoxynol 40 would be expected to function well as an [*36] ophthalmic formulation stabilizer, cannot be attributed to the state of the art at the time the 493 inventions were made. Neither the test results upon which Dr. Mitra based his conclusions, nor any similar test results, were known at the time of the patented inventions. The only data in evidence comparing the performance of Octoxynol 40 to surfactants disclosed in the prior art patents prior to the time of the patented inventions is the data from Ms. Lidgate's tests comparing the performance of Octoxynol 40 with the performance of Tween 80 and Myrj 52-other micelle-forming, non-ionic surfactants, which Dr. Mitra opined should perform "equally well." That data shows that Octoxynol 40 at a concentration of 0.004% outperforms Tween 80 and Myrj 50 at the significantly higher concentration of 0.01%. (Trial Ex. 24 at SYN0000280.)

58. In addition to the fact that Defendants' test results conducted years after the prosecution of the *493 patent* are not relevant to the expectations of those skilled in the art at the time of the patented inventions, those results are also entitled only to limited weight due to the fact that a variety of grades, sources, or types of ingredients were not [*37] tested. Moreover, because the homolog content of the BAC used in a formulation has a significant effect on the degree of complexation between ketorolac tromethamine and BAC, Defendants cannot show that the results of their tests would have been the same had a different grade of BAC been used. Likewise, Defendants cannot show that the results of their tests would have been the same had a different source of ketorolac tromethamine been used. Finally, Defendants cannot show that the results of their tests would have been same had all carboxyl group-containing NSAIDs or all quaternary ammonium preservatives been tested.

59. Defendants further failed to establish that the ingredients used in their tests were substantially similar to the ingredients used by the Syntex researchers at the time of the application for the *493 patent*. Therefore, the Court accords only limited weight to the results of tests that used ingredients that may have been different from those available at the time of the patent application.

60. Taking the foregoing findings into consideration, the Court finds that Defendants have failed to overcome the Plaintiffs' showing that the patented inventions produced [*38] unexpected results. This finding supports a conclusion that the patented inventions are non-obvious.

6. Motivation to Combine

61. In its December 29 Order, the Court found that the three prior art references asserted by Defendant -- Waterbury, Gilbert, and Han -- teach away from the use of Octoxynol 40 in an ophthalmic formulation. (Doc. # 350 at 141.) In its opinion remanding the case to this Court, the Federal Circuit directed the Court to reconsider whether Defendants have adduced clear and convincing evidence that there would have been a motivation to combine these references with the understanding that the references do not teach away from the use of Octoxynol 40. *Syntex, 407 F.3d at 1380.*

62. Reconsidering this issue, while the prior art references may not teach away from the use of Octoxynol 40 in an ophthalmic formulation, the record fails to establish by clear and convincing evidence that any of the references suggest, teach, or motivate use of Octoxynol 40 in an ophthalmic formulation. Particularly, Waterbury expressly teaches the use of Polysorbate 80. Han, in comparison, teaches the use of nonionic surfactants, generally. Gilbert discloses [*39] ophthalmic formulations that may contain a stabilizer, only some of which are nonionic surfactants. Thus, the references relied upon by Defendants, whether examined in isolation or collectively, would not have suggested a motivation to combine to one skilled in the art at the time of the patent application.

63. Defendants rely heavily upon the testimony of Dr. Mitra to support their argument that there would have been a motivation to substitute Octoxynol 40 for any of the surfactants disclosed in the Waterbury, Gilbert, and Han patents at the time of the *493 patent* inventions. Specifically, Defendants proffer Dr. Mitra's testimony that because "Octoxynol 40 was very well known in [the] cosmetic industry and has been used in many products," it "will be easy" to substitute Octoxynol 40 for the Polysorbate 80 of the Waterbury patent. (R.T. 1143:13-1144:3.)

64. Dr. Mitra testified that one would be motivated to substitute Octoxynol 40 for Polysorbate 80 based on his theory that all non-ionic water-soluble surfactants work equally well in stabilizing solutions made up of an NSAID and a quaternary ammonium preservative. (R.T. 1035:25-1038:18.)

65. In arguing that all surfactants [*40] work equally well, Defendants point to statements in Dr. Mitra's expert report that the Federal Circuit identified as potentially relevant to the issue of "unexpected results." *See Syntex, 407 F.3d at 1381* nn. 10 & 11. Defendants

argue that these statements are relevant to the separate issue of a motivation to combine.

66. For example, Dr. Mitra stated in his expert report 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 as 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." (Trial Ex. SI 348 (quoted in *Syntex, 407 F.3d at 1381 n.11*).)

67. Reviewing the Federal Circuit's Opinion, there is some ambiguity in the Circuit's language as to whether it determined that statements in Dr. Mitra's expert report are relevant to the motivation to combine issue. As the Court interprets the Federal Circuit's decision, the Circuit did not hold that these statements are relevant to the issue of motivation to combine, but, rather, [*41] that they are *potentially* relevant to unexpected results. *Syntex, 407 F.3d at 1381*. Even assuming the statements are relevant on the motivation to combine issue and are part of the pages admitted during trial, the Court accords them little probative weight. Particularly, contrary to Dr. Mitra's statement, the Waterbury patent does not discuss any problem of interaction or complexation between BAC and ketorolac tromethamine, and does not include Polysorbate 80 in an example formulation, and therefore does not show "that the non-ionic surfactant Polysorbate 80 solubilizes BAC."

68. Further, the Court finds Dr. Mitra's opinion that all water-soluble non-ionic surfactants would have worked equally well in the patented formulations unpersuasive for several reasons.

69. First, Defendants' experiments that provided the basis for Dr. Mitra's opinions regarding the "substitutability" of non-ionic water-soluble surfactants were all conducted years after the filing of the *493 patent* applications. (R.T. 1004:16-19.) Defendants offered no evidence that the results of any like experiments were known at the time of the patented inventions. The experiments therefore [*42] are not probative of the knowledge of one of ordinary skill at the time of the inventions.

70. Second, Dr. Mitra's opinion that all water-soluble non-ionic surfactants work equally well also lacks evidentiary support because the experiments offered by Defendants at trial in support of his opinion suffer from critical methodological flaws. In particular, the stability of a solution of ketorolac tromethamine and BAC will be heavily dependent on the type of BAC that is used. Because BAC is not a pure substance, but is made up of a mixture of "homologs," *i.e.*, molecules that are similar but that have varying lengths, the source of the particular BAC that is used will have a significant effect on the concentrations of ketorolac tromethamine and BAC at which a complex is formed. (R.T. 1647:24-1649:1, 1670:2-1676:4; Trial Ex. 306.) The tests presented by Defendants that evaluated the effect of Octoxynol 40 and/or compared the effect of Octoxynol 40 with the effects of other surfactants all used BAC and ketorolac tromethamine from a single source. Novex Pharma, in general, did not account for the possibility that the particular homolog content of the BAC that it was affecting the [*43] stability of the formulations or whether any lot-to-lot variability in the ketorolac tromethamine was having an effect. On the one occasion on which Dr. Mitra tested the effect of using different types of BAC, he found that the type of BAC used had a significant effect on the degree of complexation between ketorolac tromethamine and BAC. (R.T 1202:17-1207:25.) Similarly, a test performed by Cynthia Pulsipher, a scientist at Syntex, confirmed that variability between lots of ketorolac tromethamine could affect the stability of the resulting formulation. (Trial Ex. 209; R.T. 186:25-187:7, 196:2200:12, 381:3-392:5.)

71. Because Defendants have failed to show that the ingredients used in the tests performed by Dr. Mitra and Novex Pharma were substantially similar to the ingredients used by the Syntex researchers the Court accords their test results evaluating the effect of Octoxynol 40 and/or comparing the effect of Octoxynol 40 with the effects of other surfactants only to limited weight. Particularly, because the homolog content of the BAC used in a formulation has a significant effect on the degree of complexation between ketorolac tromethamine and BAC, Defendants cannot show that [*44] the results of their tests would have been the same had a different grade of BAC been used. Likewise, Defendants cannot show that the results of their tests would have been the same had a different source of ketorolac tromethamine been used. Cumulatively, these weaknesses in Defendants' tests significantly undermine the validity of their data.

72. Dr. Mitra's critique of Syntex's testing relating to turbidity is also unpersuasive. Specifically, Dr. Mitra accounted for the variation in the turbidity results observed by the Syntex scientists by opining that, as more tromethamine is added to a solution containing ketorolac tromethamine and BAC, the tromethamine ions drain the ketorolac ions from the solution, forcing the ketorolac/BAC precipitate to dissolve. (R.T. 1010:14-1013:20.)

73. Dr. Stella, however, testified that this theory was "fundamentally unsound." (R.T. 1716:9-1717-4.) Specifically, Dr. Stella pointed out that more tromethamine ions could not be added to the solution without, at the same time, adding more ketorolac ions. Therefore, the

continued addition of ketorolac tromethamine would not serve to drain the ketorolac ions from the solution and would not shift [*45] the equilibrium such that the precipitate would dissolve. (R.T. 1716:9-1717:19.) Dr. Mitra did not provide a viable explanation as to how more tromethamine ions would be introduced to the solution without the accompanying ketorolac ions. His inability to proffer such an explanation seriously undermines the persuasiveness of his theory with respect to Syntex's tests.

74. With respect to Dr. Mitra's opinion that non-ionic, water-soluble surfactants act alike, the Court also takes notice of evidence in the record calling this opinion into question. Specifically, the "Surfactant Systems" treatise lists data showing that different surfactants can have widely different abilities to solubilize the same compound. (Trial Ex. 033 at 343, Table 6.23(a).) In fact, that data shows for a particular compound a 17-fold variation in the ability of several different surfactants (including four types of polysorbate) to solubilize the compound in question. (*Id.* (showing, in the right-hand column, solubilities of from 0.04 to 0.68 moles of compound per mole of surfactant).) Such a wide variation in the ability to solubilize demonstrates that all water-soluble, micelle-forming, non-ionic surfactants [*46] do not perform alike. Furthermore, the "Surfactant Systems" treatise explicitly recognizes the presence of "variations in the properties of commercial surface-active agents," *id.* at 344, confirming the variability in the performance of different surfactants.

75. Plaintiffs have also offered Dr. Stella's testimony which contradicts Dr. Mitra's theory regarding the substitutability of surfactants. Notably, Dr. Stella testified that a surfactant's critical micelle concentration, *i.e.*, the concentration at which a surfactant forms micelles, varies depending on both the structure of the surfactant -- namely, the length of the alkyl chain groups and the polarity of the head group -- and the structural elements of the material the surfactant is attempting to solubilize. (R.T. 1692:5-23.) This critical micelle concentration will also vary with temperature, with the addition of electrolytes, and with the presence of other ingredients in a formulation. (R.T. 1846:24-1848:1 (Mitra).) Because of the high variability and sensitivity of surfactants' critical micelle concentrations, Dr. Stella testified that different surfactants will differ widely in their abilities to stabilize a given [*47] structure or solution. (R.T. 1692:24-1693:9.)

76. Dr. Stella also criticized Dr. Mitra's opinion for failing to take into account how the variations in other parameters, such as differences in BAC and environmental factors, affected when turbidity and haziness cleared. (R.T. 1717:5-9.)

77. Dr. Stella further opined that Dr. Mitra's theory failed to explain the variations in the test results because it did not take into account the effect of the variations seen between the Syntex data, the Novex data, and Dr. Mitra's own data. (R.T. 1717:11-19.)

78. Overall, as the foregoing findings illustrate, Dr. Mitra's opinions are based on tests that post-date the filing of the *493 patent* applications; suffer from methodological flaws, and are directly contradicted by Dr. Stella's testimony. Taken together, these factors undermine the validity of Dr. Mitra's opinions and compel the Court to find that his testimony is not credible. In contrast, the Court finds Dr. Stella's opinions and supporting rationales to be persuasive. The Court therefore rejects Dr. Mitra's testimony on whether a motivation to combine existed.

7. The Dependent Claims of the 493 Patent

79. [*48] The dependent claims of the *493 patent* disclose more detailed inventions than the independent claims, including: pharmaceutical compositions containing specific quaternary ammonium preservatives and NSAIDS (claims 2-3); pharmaceutical compositions containing specific proportions of chelating agents and other ingredients (claims 4-7); specific method claims (claims 9-14); and a preservative system containing BAC and a preservative (claim 16). (Trial Ex. 001.)

80. The subjects of the dependent claims-the identity and concentration of the NSAIDs, the identity and concentration of the preservative, the identity, presence and concentrations of chelating agents and salt, and pH-all have significant effect on the stability and antimicrobial effectiveness of the ophthalmic solution. (R.T. 1636:11-1637:19, 1642:23-1645:9, 1662:9-1664:3, 1697:4-1698:4.) There was no evidence introduced that the inventions of the dependent claims of the *493 patent* would have been obvious to a person of ordinary skill in the art at the time of their invention.

8. Commercial Embodiment of the Patented Inventions: ACULAR(R)

81. Syntex submitted an NDA to the FDA, pursuant to Section 505(b) of [*49] the Federal Food, Drug, and Cosmetic Act, seeking approval to market and sell a 0.5% ketorolac tromethamine ophthalmic solution, the drug that became ACULAR(R). In 1992, the FDA approved ACULAR(R) for the treatment of ocular itch associated with seasonal allergic conjunctivitis. In 1997, the FDA approved ACULAR(R) for use in the treatment of postoperative inflammation. (R.T. 1272:9-1274:15.)

82. ACULAR(R) is a sterile isotonic aqueous solution with a pH of 7.4. ACULAR(R) contains 0.5% wt/vol ketorolac tromethamine; 0.01% wt/vol BAC; 0.007%

wt/vol Octoxynol 40; 0.1% wt/vol edetate disodium, a chelating agent; 0.79% wt/vol sodium chloride; hydrochloric acid and/or sodium hydroxide to adjust the pH; and purified water. ACULAR(R) includes each element of each of Claims 1-7 and 15-16 of the *493 patent*, and the uses of ACULAR(R) include each element of each of Claims 8-14 of the *493 patent*. Claim 7 of the *493 patent* claims the ingredients of ACULAR(R) exactly, and Claim 14 of the *493 patent* claims the use of ACULAR(R) exactly. (Trial Ex. 085; R.T. 1534:10-1536:14.)

83. In 1994, within one year of ACULAR(R)'s entry into the ophthalmic anti-inflammatory market, ACULAR(R)'s net [*50] sales were over $ 18 million. In 1995, ACULAR(R)'s net sales rose to over $ 21 million, and by 1999, its net sales had risen to over $ 46 million. In 2001, ACULAR(R)'s net sales were over $ 58 million. All told, during the period from ACULAR(R)'s introduction in 1993 through 2001, ACULAR(R) garnered over $ 291 million in net sales and captured a 36.1% market share among ophthalmic anti-inflammation drugs. (Trial Exs. 090,091; RT. 1541:13-1555:14, 1558:23-1562:18.)

84. ACULAR(R) has consistently outperformed ACULAR PF(R), a formulation of ACULAR(R) that contains the same previously-patented active ingredient as ACULAR(R), but does not contain BAC or Octoxynol 40. (Trial Exs. 092, 095, 096; R.T. 1566:5-12; *id.* at 1576:3-6.)

85. ACULAR(R) has also far outperformed its chief competitor drug, Voltaren Ophthalmic(R), which appeared in the marketplace three years prior to ACULAR(R). Voltaren Ophthalmic(R), like ACULAR(R), is an ophthalmic NSAID, but Voltaren Ophthalmic(R) contains a different active ingredient than the previously-patented ketorolac tromethamine contained in ACULAR(R). Voltaren Ophthalmic(R) also does not contain Octoxynol 40. (Trial Exs. 091, 092, 095, 096; [*51] R.T. 1561:20-1562:18, 1577:8-14.)

86. Despite lagging behind ACULAR(R), Voltaren Ophthalmic(R) has consistently far outperformed the only other drug containing the previously-patented active ingredient contained in ACULAR(R), ACULAR PF(R). (Trial Exs. 091, 092, 095, 096.)

87. Allergan entered into an exclusive distribution arrangement with Syntex for the 0.5% ketorolac tromethamine ophthalmic formulation on October 22, 1990, before the *493 patent* issued. Allergan has paid to Syntex more than $ 133 million in royalties under this agreement. (Trial Exs. 083, 084; R.T. 1537:20-1540:24.)

88. Defendants' ANDA 76-109 specifies that Defendants seek to market a drug that is identical to ACULAR(R) in its composition, preservative system, and intended uses. (Trial Ex. 058.)

9. Summary of Factual Findings

In sum, based on its review of the record evidence, including the *493 patent*, the prior art references, and the testimony and exhibits presented at trial, and considering the directives that the Federal Circuit set forth in its remand order, the Court finds: (a) the prior art references do not suggest a motivation to combine; (b) Plaintiffs have shown that the inventions [*52] in the *493 patent* produced unexpected results; and (c) Dr. Mitra's testimony does not establish that a motivation to combine existed.

B. Conclusions of law

1. Legal Standard -- Obviousness

89. *Section 103(a) of the Patent Act* states that "[a] patent may not be obtained . . . 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." *See KAO Corp. v. Unilever U.S., Inc., 441 F.3d 963, 968 (Fed. Cir. 2006).*

90. "Because patents are presumed to be valid, *see 35 U.S.C. § 282*, an alleged infringer seeking to invalidate a patent on obviousness grounds must establish its obviousness by facts supported by clear and convincing evidence." *KAO Corp., 441 F.3d at 968* (citing *Apotex USA, Inc. v. Merck & Co., 254 F.3d 1031, 1036 (Fed. Cir. 2001)).*

91. Obviousness is a legal determination based on the following factual inquiries: (1) the scope and content of the prior art; (2) the differences between the claimed invention [*53] and the prior art; (3) the level of ordinary skill in the pertinent art; and (4) secondary considerations, if any, of non-obviousness, such as commercial success, long-felt but unsolved need, failure of others, copying, and unexpected results. *See McNeil-PPC, Inc. v. L. Perrigo Co., 337 F.3d 1362, 1368 (Fed. Cir. 2003)* (citing *Graham v. John Deere Co., 383 U.S. 1, 17, 86 S. Ct. 684, 15 L. Ed. 2d 545 (1966)).*

92. The analysis under *35 U.S.C. § 103* "requires the oft-difficult but critical step of casting the mind back to the time of the invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field." *In re Dembiczak, 175 F.3d 994, 999 (Fed. Cir. 1999).* Courts "cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention." *Ecolochem, Inc. v. S. Cal. Edison Co., 227 F.3d 1361, 1371 (Fed. Cir. 2000)* (quoting *In re Fine, 837 F.2d 1071, 1075 (Fed. Cir.*

1988)). "[C]ase law makes clear that the best defense against hindsight-based obviousness analysis [*54] is the rigorous application of the requirement for a showing of a teaching or motivation to combine the prior art references" *Id.* "Combining prior art references without evidence of such a suggestion, teaching, or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability-the essence of hindsight." *In re Dembiczak, 175 F.3d 994 at 999.*

93. Moreover, finding the elements of the patented invention in the prior art is simply the beginning of the analysis. The Federal Circuit cautions:

> As this court has stated, "virtually all [inventions] are combinations of old elements." Therefore an examiner may often find every element of a claimed invention in the prior art. If identification of each claimed element in the prior art were sufficient to negate patentability, very few patents would ever issue. Furthermore, rejecting patents solely by finding prior art corollaries for the claimed elements would permit an examiner to use the claimed invention itself as a blueprint for piecing together elements in the prior art to defeat the patentability of the claimed invention. Such an approach would [*55] be "an illogical and inappropriate process by which to determine patentability."

In re Rouffet, 149 F.3d 1350, 1357 (Fed. Cir. 1998) (quoting *Envtl. Designs, Ltd. v. Union Oil Co., 713 F.2d 693, 698 (Fed. Cir. 1983)* and *Sensonics, Inc. v. Aerosonic Corp., 81 F.3d 1566, 1570 (Fed. Cir. 1996))* (citations omitted).

94. What is "[c]ritical to the analysis is an understanding of the particular results achieved by the new combination." *Gillette Co. v. S.C. Johnson & Son, Inc., 919 F.2d 720, 725 (Fed. Cir. 1990)* (quoting *Interconnect Planning Corp. v Feil, 774 F.2d 1132, 1143 (Fed. Cir. 1985))*. As the Federal Circuit held in *Gillette*, with respect to a chemical composition for a shaving gel: "There is no question that each component of [the patented] composition was separately known in the prior art. What was not known or suggested, however, was the composition that resulted from the combination of those components, and its unique properties." *Id. at 724-725.*

95. Defendants' burden of establishing obviousness in this case is particularly high because all of the prior art references [*56] asserted by Defendants at trial were before the examiner. *See Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc., 796 F.2d 443, 447 (Fed. Cir. 1986)* ("[W]hen the prior art before the court is the same as that before the PTO, the burden on the party asserting invalidity is more difficult to meet.")

96. In general, however, the Court is not bound by the PTO's assessment of the prior art. *See Kingsdown Med. Consultants, Ltd. v. Hollister Inc., 863 F.2d 867, 872 (Fed. Cir. 1988)* ("The district court is not, of course, bound by either the examiner's rejection in the parent application or the examiner's allowance in the continuation application."); *Lindemann Maschinenfabrik GMBH v. American Hoist and Derrick Co. 730 F.2d 1452, 1460 (Fed. Cir. 1984)* ("Though the courts will give due respect to the examiner's evaluation of prior art, they are not of course bound thereby.") For example, the Court is not bound by the statement by the examiner that the inventions of the *493 patent* would have been obvious absent a showing of unexpected results. (SYN0000049.)

97. To prove obviousness, it is insufficient to demonstrate that the separate [*57] elements of the invention existed in the prior art. Rather, there must be some teaching or suggestion in the prior art to combine those elements, *see Arkie Lures, Inc. v. Gene Larew Tackle, Inc., 119 F.3d 953, 957 (Fed. Cir. 1997)*. "[A] showing of a suggestion, teaching, or motivation to combine the prior art references is an essential evidentiary component of an obviousness holding.'" *Brown & Williamson Tobacco Corp. v Philip Morris Inc., 229 F.3d 1120, 1124-25 (Fed. Cir. 2000)* (quoting *C.R. Bard, Inc. v M3 Systems Inc., 157 F.3d 1340, 1352 (Fed. Cir. 1998))*. "[T]here must be some suggestion, motivation, or teaching in the prior art that would have led a person of ordinary skill in the art to select the references and combine them in a way that would produce the claimed invention." *Karsten Mfg. Corp. v Cleveland Golf Corp.; 242 F.3d 1376, 1385 (Fed. Cir. 2001)*. The showing of a suggestion, teaching or motivation to combine references "must be clear and particular." *In re Dembiczak, 175 F.3d at 999.*

98. The burden of proving a motivation to combine is an element of the accused infringer's [*58] *prima facie* case that the patent is invalid for obviousness. *Tec Air, Inc. v. Denso Mfg. Michigan Inc. 192 F.3d 1353, 1359-60 (Fed. Cir. 1999)* ("To establish a *prima facie* case of obviousness, Denso must show some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references.").

99. A patent challenger's burden to provide clear and convincing evidence of a motivation to combine the prior art references to arrive at the patented inventions is not

lessened in the context of patents concerning chemical compounds. Rather, "[f]or a chemical compound, a *prima facie* case of obviousness requires structural similarity' between claimed and prior art subject matter . . . where the prior art gives reason or motivation to make the claimed compositions." *Yamanouchi Pharm. Co., Ltd. v. Danbury Pharmacal, Inc., 231 F.3d 1339, 1343 (Fed. Cir. 2000)* (quoting *In re Dillon, 919 F.2d 688, 692 (Fed. Cir. 1990))*.

100. Furthermore, "an obviousness determination requires not only the existence of a motivation [*59] to combine elements from different prior art references, but also that a skilled artisan would have perceived a reasonable expectation of success in making the invention via that combination." *Medichem, S.A. v. Rolabo, S.L., 437 F.3d 1157, 1165 (Fed. Cir. 2006)*.

2. The Inventions of the 493 Patent Produced Unexpected Results.

101. This Court previously concluded that the patented inventions produced unexpected results. (Doc. # 350 at 153.) In its opinion remanding the case to this Court, the Federal Circuit directed this Court to reconsider that finding in light of the prosecution history and the testimony of Dr. Mitra. In particular, the Federal Circuit directed this Court to reevaluate the criticisms by the first examiner of the data comparing Octoxynol 40, Tween 80, and Myrj 52 and to reconsider the fact that, during prosecution, the applicants did not submit Ms. Lidgate's results showing that "octoxynol 12.5 and Octoxynol 40 produced test samples that looked equivalent at all temperatures.'" *Syntex, 407 F.3d at 1382-83*. The Federal Circuit also instructed this Court to consider Dr. Mitra's testimony regarding the substitutability [*60] of various surfactants in connection with the unexpected results inquiry. *Id. at 1380-82*.

102. As noted above, the examiner of Application No. 07/096,173 criticized the data comparing Octoxynol 40, Tween 80, and Myrj 52 for four reasons: (1) the data did not compare Octoxynol 40 to the surfactants of the primary references; (2) the concentration of Octoxynol 40 was greater than the concentrations of the other surfactants; (3) the data was not commensurate with the then-pending claims, which did not set proportions for the components of the formulations; and (4) the data was not in declaration form.

103. The data in the prosecution history showing that Octoxynol 40 outperformed Tween 80 and Myrj 52 is persuasive on the issue of unexpected results and is not rendered less so by any of the criticisms on the part of the examiner of the 07/096,173 application.

104. The Court has also considered Ms. Lidgate's test results regarding Octoxynol 12.5 and concludes that they do not undermine a conclusion that the patented inventions did produced unexpected results. First, even if Octoxynol 12.5 were found to perform as well in the patented formulations as Octoxynol [*61] 40-an assumption that cannot be confirmed due to the absence of antimicrobial data regarding Octoxynol 12.5-this would not detract from the unexpected results demonstrated by the data comparing Octoxynol 40, Tween 80, and Myrj 52. In other words, it would still be unexpected to find that Octoxynol 40 outperformed these other well-known surfactants, and the record does not contain persuasive evidence establishing that other surfactants, such as Octoxynol 12.5, would have had the same result. Second, while Dr. Lidgate's test results allowed her to conclude that Octoxynol 12.5 and Octoxynol 40 were equivalent from a visual perspective, the data was too preliminary to allow her to make any further conclusions regarding their equivalence.

105. Defendants have argued that Ms. Lidgate's experiments that led to the submission of the Lidgate Declaration improperly lacked a "control formulation"-that is, a formulation to which other formulations are compared. In fact, the formulation containing Octoxynol 40 was the formulation that other formulations were being compared against, and it therefore acted as the "control" formulation in the experiments. (R.T. 621:6-622:17.)

106. Dr. Mitra's [*62] testimony that a surfactant's possession of micelle-forming and non-ionic properties would necessarily lead that surfactant to have stabilizing abilities, and that therefore it was to be expected that Octoxynol 40 would function "equally [as] well" as other micelle-forming, non-ionic surfactants in stabilizing ophthalmic formulations, R.T. at 1016:1-1018:15; *id.* at 1054:6-24; *id.* at 1122:14-1123:13; *id.* at 1129:3-16, fails on two levels to support a finding that Octoxynol 40's performance was not expected. First, if the state of knowledge at the time the inventions was that all micelle-forming, non-ionic surfactants would work "equally well," then Plaintiffs' evidence of the results of testing carried out by Ms. Lidgate-showing that Octoxynol 40 outperformed two other much more well-known micelle-forming, non-ionic surfactants-is highly unexpected. (R.T. 695:1-701:14; Trial Exs. 204, 205.) Moreover, the corollary to Dr. Mitra's substitutability theory, namely that Octoxynol 40 would be expected to function well as an ophthalmic formulation stabilizer, cannot be attributed to the state of the art at the time the 493 inventions were made. As noted above, neither the test [*63] results upon which Dr. Mitra based his conclusions, nor any similar test results, were known at the time of the patented inventions. The only data in evidence comparing the performance of Octoxynol 40 to surfactants disclosed in the prior art patents prior to the time of the patented inventions is the data from Ms. Lidgate's tests

comparing the performance of Octoxynol 40 with the performance of Tween 80 and Myrj 52-other micelle-forming, non-ionic surfactants, which Dr. Mitra opined should perform "equally well." That data shows that Octoxynol 40 at a concentration of 0.004% outperforms Tween 80 and Myrj 50 at the significantly higher concentration of 0.01%. (Trial Ex. 24 at SYN0000280.)

107. In addition to the fact that Defendants' test results conducted years after the prosecution of the *493 patent* are not relevant to the expectations of those skilled in the art at the time of the patented inventions, those results are also entitled only to limited weight due to the fact that a variety of grades, sources, or types of ingredients were not tested. Moreover, because the homolog content of the BAC used in a formulation has a significant effect on the degree of complexation between [*64] ketorolac tromethamine and BAC, Defendants cannot show that the results of their tests would have been the same had a different grade of BAC been used. Likewise, Defendants cannot show that the results of their tests would have been the same had a different source of ketorolac tromethamine been used. Finally, Defendants cannot show that the results of their tests would have been same had all carboxyl group-containing NSAIDs or all quaternary ammonium preservatives been tested.

108. Defendants further failed to establish that the ingredients used in their tests were substantially similar to the ingredients used by the Syntex researchers at the time of the application for the *493 patent*. Therefore, the Court accords only limited weight to the results of tests that used ingredients that may have been different from those available at the time of the patent application.

109. Accordingly, the Defendants have failed to overcome the Plaintiffs' showing that the patented inventions produced unexpected results. This finding favors a conclusion that the inventions are non-obvious.

3. Motivation to Combine

110. In its prior order, the Court found that there could be no [*65] motivation to combine or modify the three prior art references asserted by Defendant-Waterbury, Gilbert, and Han-because those references teach away from the use of Octoxynol 40 in an ophthalmic formulation. (Doc. # 350 at 141.) In its opinion remanding the case to this Court, the Federal Circuit directed the Court to reconsider whether Defendants have adduced clear and convincing evidence that there would have been a motivation to combine these references with the understanding that the references do not teach away from the use of Octoxynol 40. *Syntex, 407 F.3d at 1380.* Accordingly, the Court will reassess the facts presented above to determine whether Defendants have proven that there would have been a motivation to combine or modify the prior art to arrive at the patented inventions notwithstanding the fact that Waterbury, Gilbert, and Han do not teach away.

111. The Court finds that a person of ordinary skill in the art at the time of the inventions of the *493 patent* would not have had a motivation to combine the Waterbury, Gilbert, or Han patents with the *McCutcheon's* reference. The Court also finds that a person of ordinary skill in the art at the time [*66] of the inventions of the *493 patent* would not have had a reasonable expectation of success from doing so. Plaintiffs' expert, Dr. Stella, testified that there was nothing in *McCutcheon's* that would have motivated one of ordinary skill in the art to combine it with the other prior art references to arrive at the patented inventions. Defendants offered no evidence or testimony regarding *McCutcheon's*. Moreover, because *McCutcheon's* discloses the use of Octoxynol 40 only in the context of mixing non-water-miscible materials with water, *McCutcheon's* fails to provide any expectation that Octoxynol 40 could be successfully used to stabilize solutions that do not contain an oil-based component. There is nothing in *McCutcheon's* that provides any expectation that Octoxynol 40 could successfully stabilize the interaction of an NSAID and a preservative or that Octoxynol 40 could safely be used in an ophthalmic formulation.

112. Nor is there any motivation to modify the teachings of the Waterbury, Gilbert or Han patents to substitute Octoxynol 40 for the surfactants disclosed in those references. There is nothing in these patents that suggests that one should search for [*67] a substitute surfactant, or that discloses a functional equivalency between Octoxynol 40 and other water-soluble, micelle-forming, non-ionic surfactants-or among all surfactants possessing these properties. Defendants improperly argue that the only "difference" between the inventions of the *493 patent* and the prior art-Octoxynol 40-would have been suggested by prior art references disclosing other surfactants such as the Polysorbate 80 "disclosed" in the Waterbury patent. This focus on the "difference" between the patented invention and the prior art is a legally improper use of hindsight:

> What we stressed in *Kimberly-Clark*, and have repeated many times since, was that *35 U.S.C. § 103* requires analysis of a claimed invention as a whole.
>
> It is true that [the claimed invention] consists of a combination of old elements so arranged as to perform certain related functions. It is immaterial to the issue, however, that all of the elements were old in other contexts. What must be found obvious to defeat the patent is the claimed

> combination. Focusing on the obviousness of substitutions and differences, instead of on the invention as a whole, is a legally [*68] improper way to simplify the often difficult determination of obviousness.

Gillette, 919 F.2d at 724 (quoting *Kimberly-Clark Corp. v. Johnson & Johnson, 745 F.2d 1437, 1448 (Fed. Cir. 1984))* (citation omitted). Defendants' focus on Octoxynol 40 as an obvious "substitution" for, *e.g.*, Polysorbate 80, violates this fundamental tenet of the obviousness analysis.

113. This type of hindsight focus is no more permissible in the context of chemical compounds than it is elsewhere, *see Yamanouchi, 231 F.3d at 1345* (stating that "this case has all the earmarks of somebody looking at this from hindsight"), unless the prior art references disclose "functional equivalencies" between the compound used in the invention and a compound found in the prior art, or the patent challenger proves by clear and convincing evidence that those of ordinary skill in the art at the time of the patented inventions expected such functional equivalencies. *See In re Mayne, 104 F.3d 1339, 1343 (Fed. Cir. 1997)*; *In re Dillon, 919 F.2d at 692*; *cf. Rhone Poulenc Agro, S.A. v. DeKalb Genetics Corp., 272 F.3d 1335, 1357 (Fed. Cir. 2001)* [*69] ("In order to draw the *Dillon* analogy, DeKalb must demonstrate that in the relevant field of art, plant molecular biology, it was expected that constructs imparting glyphosate tolerance would have similar properties with and without a second transit peptide. DeKalb points to no evidence that demonstrates any expectation in the relevant field of art [.]"). Because Defendants have pointed to no expectations of-or prior art references disclosing-functional equivalency between Octoxynol 40 and any surfactant disclosed in the Waterbury, Gilbert or Han patents, Defendants' focus on the substitutability of Octoxynol 40 for these prior art surfactants remains an improper use of hindsight.

114. Dr. Mitra's theory-presented at trial-that all water-soluble, non-ionic surfactants should work equally well in stabilizing solutions consisting of NSAIDs and quaternary ammonium preservatives provides no support for Defendants' argument that it would have been obvious to one of ordinary skill in the art at the time of the patented inventions to substitute Octoxynol 40 for any of the surfactants disclosed in the prior art patents. Defendants adduced no evidence that anyone at the time of the [*70] patented inventions shared Dr. Mitra's opinion. In fact, the "Surfactant Systems" treatise, from 1983, showed that all water-soluble, micelle-forming, non-ionic surfactants do not perform alike. (Trial Ex. 033 at 343-44.) In order to prove motivation to modify by substitution of chemical equivalents, a patent challenger must demonstrate that in the relevant field of art at the time of the patented inventions, it was expected that different chemical compounds would have relevantly similar properties. *Rhone Poulenc, 272 F.3d at 1357.*

115. Nor did Defendants adduce any evidence that the data from any experiments similar to those offered by Defendants to support Dr. Mitra's substitutability assertions was known at the time of the patented inventions. Absent such a showing, these experiments (and Dr. Mitra's conclusory statement that all non-ionic surfactants are equally effective) are not persuasive to the question of whether there would have been a motivation to combine at the time of the patented inventions. *Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1380 n.4 (Fed. Cir. 1986)* (rejecting reliance on evidence dated after the filing [*71] date of the patent because "obviousness must be determined as of the time the invention was made"); *Richardson-Vicks Inc. v. Upjohn Co., 122 F.3d 1476, 1480 (Fed. Cir. 1997)* ("The obviousness of a patent claim is determined at the time the invention was made.' *35 U.S.C. § 103.*").

116. Defendants' reliance on Dr. Mitra's hindsight reasoning, in combination with Dr. Stella's testimony that there was no motivation to combine, *see* R.T. at 1715:17-22, constitutes substantial evidence to defeat Defendants' obviousness claim. "Expert testimony of a lack of motivation to combine and the use of hindsight by [opposing experts] constitutes substantial evidence of nonobviousness.'" *Group One, Ltd. v. Hallmark Cards, Inc., 407 F.3d 1297, 1304 (Fed. Cir. 2005)* (brackets in original) (quoting *Teleflex, Inc., v. Ficosa N. Am. Corp., 299 F.3d 1313, 1334 (Fed. Cir. 2002)).*

117. Accordingly, Defendants have failed to prove, by clear and convincing evidence, that there would have been a motivation to combine or modify the asserted prior art references to arrive at the patented inventions. As a result, Defendants [*72] have failed to make out a *prima facie* case that the *493 patent* is invalid for obviousness.

4. Objective Evidence Relating to Obviousness

118. Because Defendants have failed to prove the *prima facie* element of a motivation to combine, they have failed to prove the *493 patent* invalid for obviousness. *See Tec Air, 192 F.3d at 1359-60*; *see also Alza Corp. v. Mylan Labs., Inc., 391 F.3d 1365, 1373 n.9 (Fed. Cir. 2004)* ("Because Mylan has not made a prima facie case of obviousness, we need not address the parties' assertions regarding the district court's discussion of secondary considerations.").

119. Furthermore, Plaintiffs introduced objective evidence that strongly attests to the non-obviousness of

the inventions of the *493 patent*. In this regard, the Court has considered the objective evidence of non-obviousness, such as, for example, commercial success and industry acclaim, licensing and royalty payments, unsuccessful attempts to create the invention, long-felt need, and unexpected results. *See Apple Computer, Inc. v. Articulate Systems, Inc., 234 F.3d 14, 26 (Fed. Cir. 2000)*; *Ecolochem, Inc. v. S. Cal. Edison Co., 227 F.3d 1361, 1376-80 (Fed Cir. 2000)*; [*73] *John Charles Designs, Inc. v. Queen Int'l Design, Inc., 940 F. Supp. 1516, 1521 (C.D. Cal. 1996)*. As the Federal Circuit has noted, "evidence of secondary considerations may often be the most probative and cogent evidence in the record. It may often establish that an invention appearing to have been obvious in light of the prior art was not. It is to be considered as part of all the evidence, not just when the decision maker remains in doubt after reviewing the art." *Stratoflex, Inc. v. Aeroquip Corp., 713 F.2d 1530, 1538-39 (Fed. Cir. 1983)*. In many cases, such as in this case, the objective evidence of non-obviousness, which must be considered by the Court, includes facts that arise after the issuance of the patent and that therefore could not have been considered by the patent examiner.

5. Commercial Success of ACULAR(R)

120. Plaintiffs have submitted copious evidence that their commercial embodiment of the patented inventions, ACULAR(R), has had commercial success. See 71-74, supra.

121. A nexus between the patented inventions and commercial success is presumed to exist when the features of the patented drug are embodied in a commercially [*74] marketed product. As the Federal Circuit held in *Brown & Williamson Tobacco Corp. v. Philip Morris Inc., 229 F.3d 1120, 1130 (Fed. Cir. 2000)*, "[a] nexus between commercial success and the claimed features is required. However, if the marketed product embodies the claimed features, and is coextensive with them, then a nexus is presumed and the burden shifts to the party asserting obviousness to present evidence to rebut the presumed nexus." (emphasis added, citations omitted).

122. The Court previously found that the commercial success of ACULAR(R) favored a finding of non-obviousness in this case. See Findings of Fact and Conclusions of Law of Dec. 29, 2003 at 146-49. In its opinion remanding the case to this Court, the Federal Circuit directed the Court to reconsider that finding in light of its opinion in *Merck & Co. v. Teva Pharms. USA, Inc., 395 F.3d 1364, 1376-77 (Fed. Cir. 2005)*. In Merck, the Federal Circuit held that a patent challenger may disprove the presumed nexus between commercial success and the patented inventions by showing that the commercial success of the marketed product derived more from the fact that it contains a separately [*75] patented active ingredient than from the other features of the patent that the product as a whole embodies. Id. Here, the record evidence shows that ACULAR(R)'s commercial success derives from its embodiment of the entire combination taught by the *493 patent*, and not from the fact that its active ingredient, ketorolac tromethamine, was previously protected by another patent. This conclusion is apparent from the facts that, in terms of sales and market share, (a) ACULAR(R) has consistently outperformed ACULAR PF(R), a formulation of ACULAR(R) that contains the same active ingredient as ACULAR(R), but does not contain BAC or Octoxynol 40, and (b) Voltaren Ophthalmic(R), a competing ophthalmic NSAID that contains a different active ingredient from ACULAR(R) and ACULAR PF(R), and that also does not contain BAC or Octoxynol 40, has also far outperformed ACULAR PF(R), despite (c) lagging behind ACULAR(R). R.T. 1565:1-7; *id.* at 1567:5-12; *id.* at 1579:3-18; *id.* at 1578:8-16; Trial Exs. 091, 092, 095, 096.

123. Accordingly, the Court finds that the commercial success of ACULAR(R) favors a finding of non-obviousness.

6. Evidence of Third Party Licensing

124. The [*76] non-obviousness of the *493 patent* is further demonstrated by the fact that a third party (Allergan) entered into an exclusive distribution agreement with Syntex before the *493 patent* was issued and has paid Syntex over $ 133 million in royalties under that agreement. *See Arkie Lures, 119 F.3d at 957* (noting that licensing activity "may be highly probative of the issue of nonobviousness"). As with the evidence of commercial success, this "highly probative" evidence of royalty payments could not have been considered by the patent examiner because it had not yet occurred.

7. Inventions Satisfied a Long-Felt Need

125. The fact that the inventions satisfied a long-felt need present at Syntex for a ketorolac-based ophthalmic drug also weighs strongly in favor of a finding of non-obviousness. *See Hewlett-Packard Co. v. Tel-Design, Inc., 460 F.2d 625, 631 (9th Cir. 1972)* ("The evidence of prior unsuccessful attempts to solve the same problem established both the pressing need for such a solution as well as the fact that the solution had not been obvious to those whom the court found to be highly skilled in the pertinent art."). As stated by the [*77] Federal Circuit in a similar case:

> Pratt's extensive efforts to solve the problem of isolating the weighing system

> indicate the absence of a suggestion to combine the Brewster machine with the positive intermixing, elements of the volume machines. These efforts by Pratt tend to show that one skilled in the art would have had no reasonable expectation of success in combining the prior art machines in question. Long-felt need in the face of prior art later asserted to lead to a solution tends to negate the proposition that the combination of such prior art would have been obvious.

Micro Chem., Inc. v. Great Plains Chemical Co., Inc., 103 F.3d 1538, 1547 (Fed. Cir. 1997) (citations omitted), abrogated on other grounds by *Pfaff v. Wells Electronics, Inc., 525 U.S. 55, 119 S. Ct. 304, 142 L. Ed. 2d 261 (1998)*. The fact that Syntex scientists tried unsuccessfully for several years to formulate a ketorolac tromethamine ophthalmic solution using other surfactants and ingredients suggests that the inventions of the patent were not obvious.

126. On remand, Defendants argue that unsuccessful attempts to solve the problems addressed by the patent in suit are only relevant [*78] if they are unsuccessful attempts by scientists other than the inventors of the patent in suit. This argument fails, because in this case, the unsuccessful attempts were by scientists other than Dr. Fu and Ms. Lidgate (the inventors of the *493 patent*), such as Ms. Pulsipher. In any event, the Federal Circuit has frequently focused on the unsuccessful attempts of the patentee in its obviousness analyses. *See, e.g., Micro Chem., Inc., 103 F.3d at 1547* (holding that the patent-in-suit, invented by William C. Pratt, was non-obvious and reasoning that "Pratt's extensive efforts to solve the problem of isolating the weighing system indicate the absence of a suggestion to combine the Brewster machine with the positive intermixing elements of the volume machines"); *In re Dow Chem. Co., 837 F.2d 469, 473 (Fed. Cir. 1988)* (holding that "the five to six years of research [by the patentee] that preceded the claimed invention" supported the conclusion that "[t]he evidence as a whole does not support the PTO's conclusion that the claimed invention would have been obvious in terms of *35 U.S.C. § 103*").

127. In short, all of these [*79] secondary considerations favor a finding of non-obviousness.

8. Validity of Dependent Claims

128. "Each claim of a patent (whether in independent, dependent, or multiple dependent form) shall be presumed valid independently of the validity of the other claims; dependent or multiple dependent claims shall be presumed valid even though dependent upon an invalid claim." *35 U.S.C. § 282*. 129. On remand, Defendants raised for the first time the argument, based on dicta from *Dayco Products, Inc. v. Total Containment, Inc., 329 F.3d 1358, 1370-71 (Fed. Cir. 2003)*, that they need not prove invalidity as to each claim of the *493 patent* because the issues of validity to be resolved as to each claim are "substantially materially identical." Defendants, however, made no attempt to analyze or compare the dependent and independent claims of the *493 patent* in an attempt to prove that the issues affecting the claims are "substantially materially identical." Given that the dependent claims of the *493 patent* disclose more detailed inventions than the patent's independent claims, and that the elements claimed in the dependent claims have a major [*80] effect on the stability and antimicrobial effectiveness of the formulations, Defendants cannot meet their burden of proving the invalidity of these claims by clear and convincing evidence by simply stating, in conclusory fashion, that the dependent claims are "mere optimizations or preferred embodiments" of the independent claims. (DRB at 13-14.)

130. Because there was no evidence introduced that the more detailed inventions of the dependent claims of the *493 patent* would have been obvious to a person of ordinary skill in the art at the time of their invention, the Court finds that the inventions of the dependent claims (Claims 2-7, 9-14, and 16) would not have been obvious to such a person.

III. Conclusion as to Obviousness Challenge and Request for Injunctive Relief

131. As established by the findings of fact set forth above, Defendants have failed to prove that there would have been a motivation to combine or modify the prior art references to arrive at the patented inventions. Moreover, each of the secondary considerations favors a finding that the *493 patent* is not invalid for obviousness. Accordingly, the Court concludes that the Defendants have failed [*81] to prove by clear and convincing evidence that any claim of the *493 patent* is invalid under *35 U.S.C. § 103*.

132. *Section 271(e)(4)* provides, in relevant part:

> For an act of infringement described in [*35 U.S.C. § 271(e)(2)*]:
>
> (A) the court shall order the effective date of any approval of the drug [] involved in the infringement to be a date which is not earlier than the date of the expiration of the patent which has been infringed,

> (B) injunctive relief may be granted against an infringer to prevent the commercial manufacture, use, offer to sell, or sale within the United States or importation into the United States of an approved drug[.]

Because this Court has found that the filing of Defendants' ANDA infringed each claim of the *493 patent*, and because Defendants have not proven that any of those sixteen infringed claims is invalid or unenforceable, the Court orders as follows: (1) that the effective date of any approval of Defendants' ANDA under § 505(j) of the Federal Food, Drug & Cosmetic Act (*21 U.S.C. § 355(j)*) for the drug product "Ketorolac Tromethamine Ophthalmic Solution [*82] 0.5%" be a date not earlier than the expiration date of the 493 patent; (2) that Defendants, and all persons and entities acting in concert with Defendants, be enjoined from making, using, selling, or offering for sale in the United States, or importing into the United States, any products that infringe, induce the infringement of, or contributorily infringe the *493 patent*; and (3) that Defendants, and all persons and entities acting in concert with Defendants, be enjoined from making preparations to make, use, sell, or offer for sale Ketorolac Tromethamine Ophthalmic Solution 0.5% in the United States.

IT IS SO ORDERED.

Dated: June 2, 2006.

MARTIN J. JENKINS

UNITED STATES DISTRICT JUDGE