IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

ALCON, INC. and ALCON RESEARCH, LTD.,	)	
Plaintiffs,	)	
v.	)	Civ. No. 06-234-SLR
TEVA PHARMACEUTICALS USA, INC.,	)	
Defendant.	)	

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Richard D. Kirk, Esquire, and Ashley B. Stitzer, Esquire, of Bayard, P.A., Wilmington, Delaware. Counsel for Defendant. Of Counsel: Bruce M. Gagala, Esquire, M. Daniel Hefner, Esquire, and Douglas A. Robinson, Esquire, of Leydig, Voit & Mayer, Ltd., Chicago, Illinois.

OPINION

Dated: October 19, 2009
Wilmington, Delaware

ROBINSON, District Judge

I. INTRODUCTION

This action arises out of the filing of an Abbreviated New Drug Application (" ANDA")[1] by defendant Teva Pharmaceuticals USA, Inc. ("Teva") to market a generic version of the antibacterial drug VIGAMOX® proprietary to plaintiffs Alcon, Inc., and Alcon Manufacturing, Ltd. (now part of Alcon Research, Ltd.)[2] (collectively, "Alcon"). VIGAMOX® is a topical ophthalmic solution comprised of the active ingredient moxifloxacin hydrochloride, which is protected by, inter alia, U.S. Patent No. 6,716,830 ("the '830 patent"). Teva's ANDA asserts a "Paragraph IV Certification," and seeks approval to market a generic equivalent of VIGAMOX® prior to the expiration of the '830 patent. *See* 21 U.S.C. § 355(j)(2)(A)(vii)(IV). Alcon brought this suit against Teva on April 5, 2006, alleging infringement of the '830 patent pursuant to 35 U.S.C. § 271(e)(2)(A).[3] (D.I. 1)

A bench trial commenced February 28, 2008, principally to determine: (1) whether Teva's proposed generic equivalent ("the ANDA product") contains moxifloxacin and so infringes claim 1 of the '830 patent; and (2) whether claim 1 is invalid for anticipation, obviousness or failure to satisfy the best mode, written description, and enablement requirements of 35 U.S.C. § 112. (*Id.* at 4-5) The issues

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[1]No. 78-073.

[2]Alcon Research, Ltd. was substituted for Alcon Manufacturing, Ltd., upon the court's approval of the parties' January 22, 2008 joint stipulation. (D.I. 74)

[3]"(2) It shall be an act of infringement to submit – (A) an application under section 505(j) of the Federal Food, Drug, and Cosmetic Act or described in section 505(b)(2) of such Act for a drug claimed in a patent or the use of which is claimed in a patent[.]"

were fully briefed post-trial. (D.I. 93; D.I. 107; D.I. 108; D.I. 111; D.I. 112; D.I. 115)

The court has jurisdiction over this action pursuant to 28 U.S.C. §§ 1331, 1338(a), 2201, and 2202. Having considered the documentary evidence and testimony, the court makes the following findings of fact and conclusions of law pursuant to Fed. R. Civ. P. 52(a).

II. FINDINGS OF FACT

A. Parties

Plaintiff Alcon, Inc. is a Swiss corporation with its principal place of business in Hünenberg, Switzerland. (D.I. 79, ex. 1 at ¶ 3) It is the assignee and owner of the '830 patent. (*Id.* at ¶ 23) Plaintiff Alcon Research, Ltd., is a Delaware corporation with its principal place of business in Fort Worth, Texas. (*Id.* at ¶ 4) It is the exclusive licensee of the '830 patent. (*Id.* at ¶ 24)

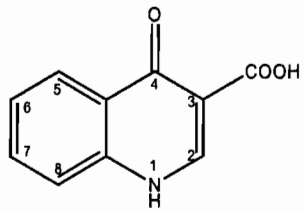
Alcon sells a topical ophthalmic pharmaceutical solution under the tradename VIGAMOX®. (*Id.* at ¶ 26) Alcon is the holder of a Food and Drug Administration ("FDA")-approved New Drug Application ("NDA") for VIGAMOX® and has listed the '830 patent, among others, in the FDA's Orange Book for VIGAMOX®. (*Id.* at ¶ 28)

Teva is a wholly-owned subsidiary of Teva Pharmaceuticals Industries, Ltd. (*Id.* at ¶ 59) Teva is a Delaware corporation with its principal place of business in Pennsylvania. (*Id.* at ¶ 5) Teva engages primarily in the manufacturing and marketing of generic drugs.

B. Moxifloxacin

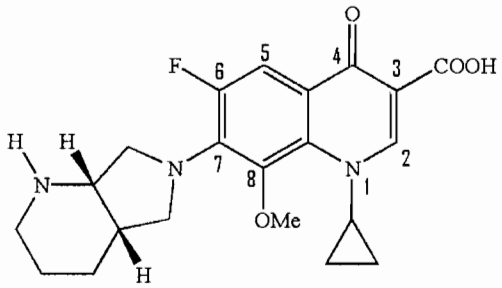
Quinolone carboxylic acids, or "quinolones," are a class of antibacterial

compounds that share a common core chemical structure, depicted as follows:



(*See* PTX 2003) The numbers along the diagram of the molecule represent positions at which functional groups may attach. (D.I. 100 at 54-55) The "COOH" at the 3-position represents a carboxylic acid. (*Id.* at 55) A carboxylic acid at the 3-position, along with a nitrogen-containing carbon ring and a double-bonded oxygen, are fundamental and common aspects of all quinolone antibiotics. (*Id.*)

Prior to July 28, 1998, the World Health Organization ("WHO") proposed the international nonproprietary name ("INN") "moxifloxacin"[4] for the quinolone depicted below:



(D.I. 100 at 60; PTX 139 at 187) Moxifloxacin, like other quinolones, possesses a carboxylic acid at the 3-position, double-bonded oxygen and a nitrogen-containing fused carbon ring. (PTX 3 at col. 98, ll. 55-65) The bicyclic amine attached at the 7-

[4]WHO used the suffix "-oxacin" as the stem name for quinolones. (D.I. 100 at 62; PTX 152 at 21)

position, a feature that distinguishes moxifloxacin from other quinolones, contains two chiral carbons. Because of these two chiral carbons, there are four possible stereochemical arrangements[5] for this molecule. (D.I. 79, ex. 1 at ¶ 68) Two of these arrangements are cis isomers, and the remaining two are trans isomers.[6] (*Id.*) The two cis compounds (denoted as "S,S" and "R,R") act as mirror images of each other, thus constituting a pair of enantiomers, while the two trans compounds ("S,R" and "R,S") constitute a second pair of enantiomers. (*Id.*) Often, enantiomers will significantly differ from each other in terms of pharmocology.[7]

Moxifloxacin has an "S,S" configuration at the chiral carbons in the 7-position bicyclic amine. (*Id.* at ¶ 70) The bolded carbon-hydrogen bonds in the figure above depict this configuration, indicating that the bonds extend upward from the rest of the molecule, which exists in the plane of the page. By contrast, the carbon-hydrogen bonds at the chiral carbons of the corresponding compound with the "R,R" configuration (the "R,R enantiomer") would extend downward beyond the plane of the paper. (*Id.*) These graphical conventions are unnecessary for named structures with known stereochemistry; the name imparts such information. (D.I. 100 at 85)

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[5]While several compounds may have the same chemical formulas and connectivity, their orientation in 3-dimensional space may differ. These alternate arrangements are known as sterioisomers.

[6]"Cis" indicates here that the hydrogen atoms on the carbons shared by the two rings are on the same side of the molecule, while "trans" indicates that the hydrogen atoms on the carbons shared by the two rings are on opposite sides of the molecule.

[7]Thus making one enantiomer much more attractive to pharmaceutical companies. Indeed, there are many blockbuster single-enantiomer drugs. *See* Jonathan J. Darrow, *The Patentability of Enantiomers: Implications for the Pharmaceutical Industry*, 2007 Stan. Tech. L. Rev. 2, 7 (2007).

Bayer AG ("Bayer") began developing moxifloxacin under the guise of BAY 12-8039, the company's designation of moxifloxacin hydrochloride ("moxifloxacin HCl"). (*Id.* at 135) Bayer is the holder of U.S. Patent No. 5,607,942 (the '942 patent),[8] which claims the compound moxifloxacin[9] and its sterioisomers. (PTX 3 at col. 98, l. 51- col. 99, l. 2) BAY 12-8039 became the subject of several studies with respect to its efficacy in combating gram-positive and gram-negative bacteria. (PTX 1124; PTX 1125; PTX 137) The specification of the '942 patent itself generally describes the efficacy of the numerous compounds disclosed as "exhibit[ing] a broad antibacterial spectrum against Gram-negative and Gram-positive bacteria . . . ." (PTX 3 at col. 53, ll. 22-27)

Satisfied with the pharmaceutical potential of BAY 12-8039, Bayer filed a NDA under the tradename AVELOX® with the FDA. This application was directed towards a 400 mg tablet form of moxifloxacin. (D.I. 105 at 1052) As of 1996, BAY 12-8039 had entered into Phase II of the NDA process. (PTX 1098) However, only Phase I[10] toxicity

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[8]The '942 patent issued on March 4, 1997.

[9]Because WHO had not yet determined the INN "moxifloxacin," the '942 patent identifies the compound both by structure and systematic (IUPAC) name: 1-cyclopropyl-7-[(S,S)-2,8-diazabicyclo [4.3.0]non-8-yl] -6-fluoro-1,4-dihydro-8-methoxy-4-oxo-3- quinolinecarboxylic acid. (PTX 3 at col. 98, ll. 52-65)

[10]Phase I of the NDA process focuses upon testing the proposed drug for acute toxicity in a small, healthy audience of volunteers. (D.I. 101 at 345) Generally considered a low hurdle to clear, toxicity may not appear in Phase I at all. (*Id.*) Indeed, toxicity may remain hidden until Phase II testing, which focuses upon drug efficacy and determining the clinically appropriate dose in a larger, less robust audience, or even after the drug is approved for distribution. (*Id.*) Thus, the successful completion of Phase I trials is often poorly predictive of the existence of toxicity.

The general caveat with respect to Phase I data applies with full force to quinolones. (D.I. 103 at 908) Indeed, many quinolones that successfully completed Phase I subsequently failed to pass muster in Phase II, Phase III or the post-approval stage when unacceptable toxicities were detected. (*Id.* at 908; PTX 2025)

data for moxifloxacin was available as of September 1998. (D.I. 103 at 906-07) The FDA approved Bayer's NDA for AVELOX® on December 10, 1999. (D.I. 104 at 1051)

C. The Invention and the '830 Patent

Dr. David Stroman is a clinical microbiologist employed by Alcon who is also involved in the selection and screening of potential ophthalmic and otic compositions. (D.I. 102 at 565, 570-571) At trial, Dr. Stroman testified that, in 1998, the focus in the art was upon the need to develop efficacious treatments for intraocular infections caused by *Staphylococcus aureus*, a gram-positive bacteria, and *Pseudomonas aeruginosa*, a gram-negative bacteria. (*Id.* at 566) Alcon, specifically, sought a compound that could both treat infections caused by these pathogens and act as a prophylactic measure to prevent infection at the time of surgery. (*Id.* at 569)

Both pathogens, which cause sight-threatening infections inside the eye, displayed emerging resistance[11] to quinolone treatment. (*Id.*) However, resistance to *Pseudomonas aeruginosa* caused investigators greater concern, because it was considered the most threatening ocular pathogen. (*Id.*) Maintaining activity against *Pseudomonas aeruginosa* while enhancing activity against *Staphylococcus aureus* became objectives of the search. (D.I. 101 at 402) In 1998, ciprofloxacin,[12] the then-

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[11]If a bacterial strain becomes resistant to one quinolone, it becomes resistant to all other quinolones. (D.I. 101 at 398-99) This phenomenon is known as a "class effect." Such resistance is generated when a weak drug fails to completely eradicate the bacterium. (D.I. 103 at 877) Scientists investigating quinolones would only consider a compound viable if characterized by a certain minimum activity against the target pathogens. (D.I. 103 at 856)

[12]Marketed by Alcon under the tradename CILOXAN®, ciprofloxacin had "tremendous activity and potency against . . . *Pseudomonas aeruginosa.*" (*Id.*) It displayed less than desirable activity against *Staphylococcus aureus.* (*Id.* at 857)

state-of-the-art treatment for ophthalmic infections, served as the standard for microbiological activity against ocular pathogens. (D.I. 102 at 568; D.I. 103 at 856)

Dr. Stroman further testified that, by contrast, the medical community had no need for new treatments solely for surface infections, such as conjunctivitis.[13] (D.I. 101 at 389-91; D.I. 102 at 566-67; D.I. 103 at 844-45) Such infections held little chance of causing serious damage, were adequately controlled by existing products and often resolved without treatment. (*Id.*)

These parameters guided Dr. Stroman's analysis of roughly one hundred compounds between 1990 (when he joined Alcon) and 1998. (D.I. 102 at 570) He encountered *in vitro* data for BAY 12-8039 on a Bayer poster at the 1997 ICAAC[14] conference in Toronto. (*Id.* at 571; PTX 1098) This data indicated that, while BAY 12-8039 was more active than ciprofloxacin against *Staphylococcus aureus*, it was eight times less active against *Pseudomonas aeruginosa*. (*Id.*) Dr. Stroman left the conference with a list of 10-15 compounds that he had interest in obtaining for further analysis. (*Id.* at 572) Despite his concerns about the *in vitro* activity data, Dr. Stroman requested from Bayer a sample of BAY 12-8039. (D.I. 103 at 645; PTX 1065)

Dr. Stroman received a 10 gram sample of BAY 12-8039 on January 4, 1999. (*Id.* at 585; PTX 89) A multi-departmental investigation confirmed Bayer's *in vitro* data

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[13]Conjunctivitis, commonly referred to as "pink eye", is a surface infection of the conjunctival membrane. (D.I. 100 at 174;D.I. 101 at 389-90)

[14]The Interscience Conference on Antimicrobial Agents and Chemotherapy.

for BAY 12-8039. (D.I. 102 at 591) However, an *in vivo* test[15] of the sample painted a different picture. (D.I. 102 at 594-95) When applied as a topical ophthalmic composition, moxifloxacin was shown to treat and prevent intraocular *Pseudomonas aeruginosa* infections, including resistant strains, as effectively as ciprofloxacin, without resistance developing rapidly. (*Id.*) Furthermore, in a separate test, moxifloxacin displayed an ocular penetration[16] greater than two times that of ofloxacin,[17] the best ocular-penetrating quinolone product available. (D.I. 102 at 597-98)

On September 30, 1998, months before Dr. Stroman even received the sample of BAY 12-8039, Alcon filed U.S. Provisional Patent Application Nos. 60/102,506 ("the '506 application") and 60/102,504 ("the '504 application") with the United States Patent & Trademark Office ("PTO"). (D.I. 102 at 573) Both applications were directed towards ophthalmic compositions containing moxifloxacin. (*Id.*) This early filing was motivated in part to avoid any future proprietary struggle between Alcon and Bayer should any novel developments result from Alcon's analysis of BAY 12-8039. (*Id.* at 574) After determining that moxifloxacin met all of Dr. Stroman's search parameters while providing enhanced ocular delivery, Alcon proceeded with its prosecution of the '506 and '504 applications.

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[15]The *in vitro* data resulted from a test tube analysis of the microbiological activity of moxifloxacin. (D.I. 103 at 899) The *in vivo* test, by contrast, involved injection of the bacteria directly into the eye of a rabbit, followed by subsequent application of a moxifloxacin solution to the ocular surface. (D.I. 102 at 593) Scientists then harvested the cornea and analyzed the microbiological activity. (*Id.*)

[16]Ocular penetration refers to the desirable ability of the compound to diffuse through the protective layers of the eye.

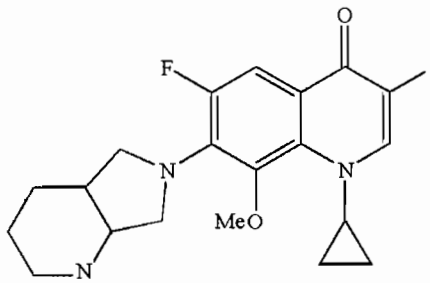
[17]Manufactured by Allergan under the tradename OCUFLOX®.

The '830 patent, entitled "Ophthalmic Antibiotic Compositions Containing Moxifloxacin," issued on April 6, 2004. (D.I. 79, ex. 1 at ¶ 15) The '830 patent ultimately matured from U.S. Patent Application No. 10/200,868 ("the '868 application"), which was filed with the PTO on July 22, 2002. (*Id.* at ¶ 16) The '868 application claims priority, through U.S. Patent Application No. 09/646,797 ("the '797 application") which was the National Stage of International Application No. PCT/US99/22622, to the '506 and the '504 applications. (*Id.* at ¶ 17) The parties agree that, for purposes of this action, the effective filing date of the '830 patent is September 30, 1998. (*Id.* at ¶ 18)

The '830 patent is directed towards topical ophthalmic antibiotic compositions. (PTX 5 at col. 1, ll. 13-21) Claim 1, the sole independent claim and the only asserted claim in this litigation, provides:

> A topical ophthalmic pharmaceutical composition comprising moxifloxacin or a pharmaceutically useful hydrate or salt thereof in a concentration of 0.1 to 1.0 wt % and pharmaceutically acceptable vehicle therefor.

(*Id.* at col. 7, ll. 29-32) The specification of the '830 patent discloses the following structure for moxifloxacin:



(*Id.* at col. 3, ll. 36-48) Notably absent from this representation of moxifloxacin is the 3-position carboxylic acid. (*Id.*) Likewise, the '830 patent omits any graphical depiction of moxifloxacin's stereochemistry. (*Id.*) However, the '830 patent provides that "[f]urther details regarding the structure, preparation, and physical properties of [m]oxifloxacin . . . are provided in U.S. Pat. No. 5,607,942." (*Id.* at col. 3, ll. 49-51)

Neither the '830 patent nor any of the applications to which it claims priority disclose moxifloxacin HCl as an embodiment of the invention. Moxifloxacin HCl, the active ingredient in both VIGAMOX® and defendant's ANDA product, is the hydrochloride salt of pure (betaine) moxifloxacin. (*Id.* at ¶ 69) When compared to moxifloxacin betaine, moxifloxacin HCl displays an enhanced solubility. (D.I. 100 at 143) Dr. Ted Taylor, Professor Emeritus of Chemistry at Princeton University, testified for plaintiffs that moxifloxacin HCl and moxifloxacin betaine will both dissolve into a solution over the claimed concentration range of the '840 patent. (*Id.* at 143) Although a solution based on moxifloxacin HCl will result in a different pH than a solution based on moxifloxacin betaine, once either form is dissolved into a solution, there is no difference[18] in microbiological activity, efficacy or toxicity. (*Id.* at 95; D.I. 104 at 1032, 1037)

At the time that Alcon filed the '506 and '504 applications, the only form of moxifloxacin known to Dr. Stroman, one of three inventors listed in the '830 patent, was that of BAY 12-8039 - moxifloxacin HCl. However, much of the correspondence between Dr. Stroman and others regarding the sample of BAY 12-8039 refer to the

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[18]Moxifloxacin HCl, an acid addition salt, will dissociate into moxifloxacin upon addition to a solution.

compound, if other than by Bayer's internal designation, simply as moxifloxacin. (PTX 402 at 1; PTX 399; PTX 89) At trial, Dr. Stroman disavowed any particular preference for the salt or betaine form of moxifloxacin, testifying that "I can't say that I ever even understood there was [a] salt form because I was focused on the active." (D.I. 102 at 577-578)

D. The ANDA Product

On or about December 25, 2005, defendant filed its ANDA.[19] (D.I. 79, ex. 1 at ¶ 30) The ANDA lists plaintiffs' VIGAMOX® as the reference drug and seeks approval for identical conditions of use. (PTX 11 at 19) Both the ANDA product and VIGAMOX® contain as the active ingredient moxifloxacin HCl (0.5 wt %). (*Id.*)

E. Asserted Prior Art

The asserted prior art relating to the '830 patent includes: (1) prior art relating to ophthalmic antibiotic compositions; and (2) prior art relating to moxifloxacin, particularly moxifloxacin HCl (i.e. BAY 12-8039). (D.I. 107 at 15)

1. Prior art relating to ophthalmic antibiotic compositions

The two state-of-the-art ophthalmic compositions in September 1998 for the treatment and prevention of ophthalmic infections were CILOXAN® and OCUFLOX® (D.I. 101 at 459; D.I. 102 at 568), both of which contained quinolones as the active pharmaceutical ingredient. (D.I. 100 at 172, 194) The prior art also included Alcon's U.S. Patent No. 5,149,693 ("the '693 patent"), which discloses ophthalmic antibiotic compositions containing tobramycin. (DTX 78; D.I. 100 at 208, 213)

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[19]The ANDA is entitled "Moxifloxacin Hydrochloride Ophthalmic Solution, 0.5% base." (D.I. 79, ex. 1 at ¶ 30)

a. CILOXAN® ophthalmic solution and ointment

CILOXAN® ophthalmic solution was approved by the FDA on December 31, 1990. (DTX 141; D.I. 100 at 195) CILOXAN® ophthalmic solution contains 0.35 wt % of ciprofloxacin hydrochloride as the active ingredient. (DTX 144; D.I. 100 at 194)

As of 1998, CILOXAN® was also marketed by Alcon as an ophthalmic ointment. (PTX 1063; D.I. 100 at 202) CILOXAN® ointment was approved by the FDA on March 30, 1998. (PTX 146; D.I. 100 at 203) It contains 0.3 wt % of ciprofloxacin hydrochloride as the active ingredient. (PTX 1063; D.I. 100 at 202-03)

b. OCUFLOX® ophthalmic solution

OCUFLOX® was marketed by Allergan, Inc., as of 1995. (DTX 159; D.I. 101 at 220) It contains 0.3 wt % of ofloxacin as its active ingredient. (DTX 159; D.I. 101 at 220-21)

c. TOBRADEX® ophthalmic suspension

TOBRADEX® ophthalmic suspension is an antibiotic composition that contains tobramycin, which is an aminoglycoside antibiotic. (DTX 145; D.I. 100 at 207, 208) Alcon manufactures TOBRADEX® ophthalmic suspension and has had it on the market since 1996. (DTX 145; D.I. 100 at 208) The active ingredients in TOBRADEX® ophthalmic suspension are tobramycin (0.3 wt %) and dexamethasone (0.1 wt %), the latter an anti-inflammatory. (DTX 145; D.I. 101 at 208)

d. The '693 patent

The '693 patent is titled "Combination of Tobramycin and Fluorometholone for Topical Ophthalmic Use." (DTX 78) It issued on September 22, 1992, and is assigned to Alcon. (*Id.*; D.I. 100 at 213) Example II of the '693 patent is

Fluorometholone acetate, USP	0.1% + 2% excess	1 mg + 2% excess
Tobramycin; Micronized, USP	0.3% + 7% excess	3 mg + 7% excess
Chlorobutanol, Anhydrous, NF	0.5% + 25% excess	5 mg + 15% excess
Mineral Oil, USP	5%	50 mg
White Petroleum, USP	QS 100%	QS 1 g

(DTX 78, Col. 2, ll. 60-65)

2. Prior art relating to moxifloxacin

a. The '942 patent

The application leading to the '942 patent was filed on March 20, 1995 as a divisional application (in a chain of divisionals) claiming priority to U.S. Patent No. 4,990,517, and issued on March 4, 1997. The specification of the '942 patent discloses numerous quinolone compounds. (PTX 5) Drawing upon the antibacterial aspect of quinolones as a class, the '942 patent details a laundry list of maladies, including "eye infections," which may be treated by the disclosed compounds. (*Id.* at col. 54, ll. 7-22) The claims of the '942 patent are directed to a specific quinolone and its four stereoisomers, one of which is moxifloxacin. (*Id.* at col. 98, l. 51-col. 99, l. 17)

b. Pre-1998 publications

Publications as of 1998 indicated that moxifloxacin displayed a more desirable resistance profile than ciprofloxacin against certain bacteria, including *Staphylococcus aureus*. (PTX 1124) However, the bacteria studied were either not identified to be ocular pathogens or, in the case of *Staphylococcus aureus*, not identified as originating from an ocular source. (*Id.*; D.I. 102 at 520-22)

Furthermore, several physical properties of moxifloxacin had been reported as of this time. Solubility data indicated that moxifloxacin could be made into a solution. (D.I. 102 at 512-13) The pharmacokinetics of moxifloxacin showed that the compound "could

effectively penetrate[ ] extravascular tissue,[20] including lung tissue." (PTX 223 at 2060) Likewise, moxifloxacin was known to penetrate the protective cerebrospinal fluid barrier of the brain. (DTX 191; D.1. 102 at 517-18)

III. CONCLUSIONS OF LAW

A. Infringement

"'It shall be an act of infringement to submit' an ANDA to the FDA seeking approval 'to engage in the commercial manufacture, use, or sale of a drug . . . claimed in a patent or the use of which is claimed in a patent before the expiration of such patent.'" *Cephalon, Inc. v. Watson Pharmaceuticals, Inc.*, 2009 WL 1838352 *7 (D. Del. Apr. 3, 2009) (quoting 35 U.S.C. § 271(e)(2)). To determine whether a composition identified in an ANDA is a composition claimed in a patent, the court conducts the familiar two-step infringement inquiry: first, the court construes the patent claims; second, it compares the construed claims to the accused product to determine whether every claim limitation is found in the accused product. *See, e.g., Roche Palo Alto LLC v. Apotex, Inc.*, 531 F.3d 1372, 1377 (Fed. Cir. 2008) (condoning use of the two-step infringement inquiry in the ANDA context). The patent owner has the burden of proving infringement and must meet its burden by a preponderance of the evidence. *SmithKline Diagnostics, Inc. v. Helena Lab. Corp.*, 859 F.2d 878, 889 (Fed. Cir. 1988) (citations omitted).

In this case, the two-step infringement inquiry is, to a degree, simplified. With one exception, the parties agree that defendant's ANDA product contains every limitation of

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[20]While "extravascular tissue" technically includes the eye, the parties dispute whether this statement would have been interpreted as indicia of ocular penetration. (D.I. 102 at 515; D.I. 103 at 952)

the '830 patent. (*See* D.I. 79, ex. 1 at ¶¶ 45, 58, 77) That one exception, or point of dispute, is whether the ANDA product contains "moxifloxacin" as it is used in claim 1, and the parties agree that the court's construction of "moxifloxacin" is dispositive of plaintiffs' infringement claim. (*See id.*) To wit, if the court construes the "moxifloxacin" disclosed in claim 1 in accordance with the general understanding of that term in the scientific community, then the ANDA product infringes, because there is no dispute that the ANDA product contains moxifloxacin. (PTX 11; D.I. 79, ex. 1 at ¶¶ 45, 58, 77) Conversely, if the court construes the "moxifloxacin" disclosed in claim 1 as being a compound other than moxifloxacin, the ANDA product does not contain all the limitations of the '830 patent and so does not infringe. The court focuses, then, on construing "moxifloxacin."

1. Claim construction generally

As a general matter, the court construes the words of a claim according to "their ordinary and customary meaning." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1313 (Fed. Cir. 2005). A claim term's "ordinary and customary meaning" "is the meaning that the term would have to a person of ordinary skill in the art in the question at the time of the invention, i.e., as of the effective filing date of the patent application." *Id.* "[T]he person of ordinary skill in the art is deemed to read the claim term not only in the context of the particular claim in which the disputed term appears, but in the context of the entire patent, including the specification." *Id.* Where "the meaning of a claim term as understood by persons of skill in the art is . . . not immediately apparent," the court turns to publicly-available sources to ascertain the meaning, including "the words of the claims themselves, the remainder of the specification, the prosecution history, and extrinsic

evidence concerning relevant scientific principles, the meaning of technical terms, and the state of the art." *Id.* at 1314 (quotation marks omitted).

2. Person of ordinary skill in the art

To determine the person of ordinary skill in the art, the court may consider various factors, including: "(1) the educational level of the inventor; (2) type of problems encountered in the art; (3) prior art solutions to those problems; (4) rapidity with which innovations are made; (5) sophistication of the technology; and (6) educational level of active workers in the field." *Envtl. Designs, Ltd. v. Union Oil Co.*, 713 F.2d 693, 696 (Fed. Cir. 1983). Courts use these factors as a guide, and the weight or significance the court ascribes to these or similar factors will depend on the case. *See id.* at 696-697; *Daiichi Sankyo Co., Ltd. v. Apotex, Inc.*, 501 F.3d 1254, 1256 (Fed. Cir. 2007).

Applying the factors in this case, the court concludes that the ordinary person of skill in the art would be a person with a Ph.D in microbiology or an M.D. with training in ophthalmology, that is, a person with knowledge of chemistry, ophthalmic pathogens, and antibiotic compounds sufficient to appreciate the relative merit of various antibiotic compositions in treating and preventing ophthalmic infections. The inventors responsible for claim 1, all of whom possess Ph.Ds in microbiology, would be typical of that person.[21] Further, the '830 patent was addressed to the problem of finding an

[21]Defendant seeks to render immaterial the formal education of the inventors because of the lack of microbiological tests performed during the development of the subject matter of the '830 patent. Such a theory wrongly suggests that the skill set of microbiologists is limited solely to physical testing, and is inconsistent with the myriad skills employed by Dr. Stroman, a microbiologist, in his assessment of the needs in the field of treating and preventing ophthalmic infections and in his selection of compounds to meet those needs.

antibiotic composition that could more effectively treat and prevent ophthalmic infections while deterring key ophthalmic pathogens from developing resistance; the person of ordinary skill in the art described above would understand the problem and whether a proffered treatment solved it. Specifically, the person of ordinary skill in the art described above would be able to analyze both the effectiveness of the antibiotic composition against the key pathogens and the composition's toxicity to humans, which ultimately determines the composition's suitability as a treatment.

Teva argues that the person of ordinary skill in the art is someone with experience solely in formulation. (D.I. 107 at 23) This argument has some intuitive appeal, since the aim of the '830 patent is, ultimately, to formulate a composition for opthalmic use. However, a formulator without knowledge of microbiology or ophthalmology would not be able to appreciate the inventive aspect of the patent, which is the selection of moxifloxacin for an ophthalmic composition, instead of some other antibiotic compound. Indeed, without these tools a formulator would be ill-equipped to assess the efficacy and resistance profile of a given treatment. *Cf. DyStar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co.*, 464 F.3d 1356, 1362 (Fed. Cir. 2006) (ordinary person of skill in the art must be "concerned" with the problems the patent seeks to address). Moreover, it is clear from the specification's sparse guidance with respect to formulation that the patent was not directed towards resolving issues in this field. Accordingly, while the person of ordinary skill in the art might have some experience with formulation, he or she will not be a formulator, but rather someone with advanced training in microbiology or ophthalmology.

3. Meaning of "moxifloxacin" to person of ordinary skill in the art

The court first addresses Teva's redefinition argument. Teva maintains that Alcon has redefined the "moxifloxacin" of claim 1 of the '830 patent to represent the compound depicted in the specification. Indeed, it is well settled that "inventor's lexicography governs" when the specification reveals a special definition for a claim term that "differs from the meaning it would otherwise possess." *Phillips v. AWH Corp.,* 415 F.3d 1303, 1316 (Fed. Cir. 2005) (en banc). Teva contends that, because the specification of the '830 patent provides an alternate meaning for the claim term "moxifloxacin" in the form of the depiction of a structurally different compound, the ordinary meaning of moxifloxacin has been displaced. (D.I. 108 at 2) Teva marshals support for its proffered meaning by pointing to a specific reference in the specification to a "new class of antibiotics." (PTX 5 at col. 1, ll. 18-19) Quinolones, Teva argues, were not a new class of antibiotics; therefore, the subject matter of the '830 patent must be directed to a different family of compounds.[22] (D.I. 108 at 4)

The court rejects Teva's proposed construction. In order for a patentee to act as his own lexicographer, any redefinition must "appear with reasonable clarity,

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[22]Teva seeks, in the alternative, to distinguish its generic moxifloxacin product on grounds of stereochemistry. (D.I. 108 at 1) Specifically, Teva points to the absence of graphical indicia of stereochemistry in the '830 patent, and asserts that Alcon has claimed a racemic mixture, or a 50/50 mixture of enantiomers, instead of just the S,S enantiomer, which is the active ingredient in both VIGAMOX® and Teva's generic product.

This is unpersuasive. That a molecule has a known stereochemistry does not require the graphical depiction of such. As discussed previously, the names of certain compounds will themselves convey such information. Moxifloxacin is one of these names. Furthermore, even the failure to graphically indicate the stereochemistry of a molecule without known stereochemistry does not mandate an interpretation that it is a racemic mixture. Indeed, scientists have indicated racemic mixtures by including, next to the structures, conventions such as RAC, (racemic), DL or RS. (D.I. 100 at 87)

deliberateness, and precision before it can affect the claim." *Abbott Labs. v. Syntron Bioresearch, Inc.*, 334 F.3d 1343, 1355 (Fed. Cir. 2003) (internal quotation marks omitted); *Renishaw PLC v. Marposs Societa' per Azioni*, 158 F.3d 1243, 1249 (Fed. Cir. 1998). The record before the court is replete with instances in which Teva's proposed construction is at odds with the specification of the '830 patent so as to cause an absence of the requisite clarity, deliberateness and precision. *See id.*

First, it is clear that the "new class of antibiotics" refers to the class of compounds depicted in the specification by formula (I).[23] Formula (I) depicts the general structure of quinolone compounds. (PTX 5 at col. 2, ll. 50-60) The specification further provides that "moxifloxacin is [the] most preferred" within the formula's class of compounds. (PTX 5 at col. 3, l. 36) Here, Teva's construction is precluded because formula (I) would not encompass a compound containing a 3-position methyl group[24] or, in the alternative, lacking a 3-position carboxylic acid.[25]

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[23]"The compositions and methods of the invention are based on the use of a new class of antibiotics." (PTX 5, at col. 1, ll. 18-19); "The antibiotics used in the compositions and methods of the present invention have the following formula: (I)." (*Id.* at col. 2, ll. 48-50); "Compositions of the present invention will contain one or more compounds of formula (I)." (*Id.* at col. 5, ll. 55-58)

[24]Teva argues that the line at the 3-position of "moxifloxacin" in the '830 patent represents a methyl group. (D.I. 108 at 13) While one convention for drawing organic molecules includes the use of lines to indicate methyl groups, using "Me" to indicate such groups is another popular practice. (D.I. 100 at 70) Generally, conventions are consistent throughout the structure. (*Id.* at 70-71) Teva has declined to comment on the presence of both conventions in the '830 patent's depiction of moxifloxacin. This, of course, militates toward the finding that a typographical error in the form of an omission, and not a methyl group, exists at the 3-position of "moxifloxacin" in the '830 patent.

[25]The 3-position may also exist as an ester, which is a pro-drug form of the active carboxylic fuctionality. (PTX 5 at col. 2, l. 48 - col. 3, l. 35)

A conflict is also readily apparent between the portion of the specification immediately below the structure and the alleged alternative meaning of moxifloxacin. The '830 patent explains, "[f]urther details regarding the structure, preparation, and physical properties of [m]oxifloxacin and other compounds of formula (I) are provided in U.S. Pat. No. 5,607,942." (*Id.* at col. 3, ll. 49-50) As stated, *supra*, the '942 patent is directed to the disclosure of numerous quinolone compounds and specifically claims the structure which would later receive the INN moxifloxacin. The '942 patent offers absolutely no guidance regarding a structure with a 3-position methyl group. Thus, the incorporation by reference to the '942 patent buttresses the conclusion that the inventors of the '830 patent did not define a novel compound that did not belong to the quinolone class.

The specification, when viewed as a whole, does not clearly, deliberately or precisely indicate that the inventors have acted upon their lexicographic license to change the meaning of moxifloxacin. *See Abbott Labs.,* 334 F.3d at 1355. The court, therefore, finds that the inventors of the '830 patent did not redefine moxifloxacin; rather, a typographical error exists at the 3-position of the structure.

This conclusion is supported by an examination of the prosecution history and all relevant extrinsic evidence. *See Phillips*, 415 F.3d at 1314. The file history of the '830 patent reveals a mutual understanding between the PTO and the inventors that moxifloxacin was a compound well known in the art. (PTX 6 at BA001-002828) Indeed, the examiner initially rejected the claims of the '797 application as anticipated by the '942 patent. (*Id.*) In traversing the rejection, Alcon explained that, while moxifloxacin was disclosed in the '942 patent, ophthalmic compositions containing moxifloxacin were

not. (*Id.* at 2839) This comports with the testimony of Dr. Stroman, who explained that the patentees were claiming a novel ophthalmic composition containing the previously known moxifloxacin and not "the use of a brand new compound in an ophthalmic composition." (D.I. 102 at 618-19)

The international naming conventions of the WHO would likewise assist in conveying the ordinary and accustomed meaning of moxifloxacin. A person of ordinary skill in the art would understand from the nomenclature alone, specifically the suffix "-oxacin," that moxifloxacin belonged to the class of quinolone antibacterial compounds. (D.I. 100 at 61; *id.* at 77) A person of ordinary skill would also understand that, because the WHO had already proposed the name "moxifloxacin" as of the priority date, moxifloxacin designated a specific structure and stereochemistry. (*Id.* at 120-21)

In view of the specification, the claims, the prosecution history and all relevant extrinsic evidence, the court concludes that a person of ordinary skill in the art would understand "moxifloxacin," as used in claim 1 of the '830 patent, to indicate the quinolone compound of the same name, whose structure, stereochemistry and other properties were well known as of the priority date.

4. Existence of infringement

Having construed "moxifloxacin" according to its ordinary and accustomed meaning, the court finds that the generic moxifloxacin product described in Teva's ANDA infringes claim 1 of the '830 patent.

B. Validity

A patent is presumed valid and the burden of proving invalidity, whether under 35 U.S.C. § 112 or otherwise, rests with the challenger. *See* 35 U.S.C. § 282. In order to

overcome this presumption, the party challenging validity bears the burden of proving, by clear and convincing evidence, that the invention fails to meet the requirements of patentability. *See Hewlett-Packard Co. v. Bausch & Lomb*, 909 F.2d 1464, 1467 (Fed. Cir. 1990). Clear and convincing evidence is evidence that "could place in the ultimate factfinder an abiding conviction that the truth of [the] factual contentions [is] 'highly probable.'" *Colorado v. New Mexico*, 467 U.S. 310, 316 (1984).

1. Anticipation

a. Legal standard

Under 35 U.S.C. § 102(b), "[a] person shall be entitled to a patent unless the invention was patented or described in a printed publication in this or a foreign country . . . more than one year prior to the date of the application for patent in the United States." The Federal Circuit has stated that "[t]here must be no difference between the claimed invention and the referenced disclosure, as viewed by a person of ordinary skill in the field of the invention." *Scripps Clinic & Research Foundation v. Genentech, Inc.*, 927 F.2d 1565, 1576 (Fed. Cir. 1991). "In determining whether a patented invention is [explicitly] anticipated, the claims are read in the context of the patent specification in which they arise and in which the invention is described." *Glaverbel Societe Anonyme v. Northlake Mktg. & Supply, Inc.*, 45 F.3d 1550, 1554 (Fed. Cir. 1995). The prosecution history and the prior art may be consulted "[i]f needed to impart clarity or to avoid ambiguity" in ascertaining whether the invention is novel or was previously known in the art. *Id.* (internal citations omitted). The prior art need not be ipsissimis verbis (i.e., use identical words as those recited in the claims) to be anticipating. *See Structural Rubber Prods. Co. v. Park Rubber Co.*, 749 F.2d 707, 716 (Fed. Cir. 1984).

A prior art reference also may anticipate without explicitly disclosing a feature of the claimed invention if that missing characteristic is inherently present in the single anticipating reference. *See Continental Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1268 (Fed. Cir. 1991). The Federal Circuit has explained that an inherent limitation is one that is necessarily present and not one that may be established by probabilities or possibilities. *See id.* That is, "[t]he mere fact that a certain thing may result from a given set of circumstances is not sufficient." *Id.* The Federal Circuit also has observed that "[i]nherency operates to anticipate entire inventions as well as single limitations within an invention." *Schering Corp. V. Geneva Pharms. Inc.*, 339 F.3d 1373, 1380 (Fed. Cir. 2003). Moreover, recognition of an inherent limitation by a person of ordinary skill in the art before the critical date is not required to establish inherent anticipation. *Id.* at 1377.

An anticipation inquiry involves two steps. First, the court must construe the claims of the patent in suit as a matter of law. *See Key Pharms. v. Hercon Labs Corp.*, 161 F.3d 709, 714 (Fed. Cir. 1998). Second, the finder of fact must compare the construed claims against the prior art. *See id.* A finding of anticipation will invalidate the patent. *See Applied Med. Res. Corp. v. U.S. Surgical Corp.*, 147 F.3d 1374, 1378 (Fed. Cir. 1998).

b. Discussion

Teva argues that the '830 patent is invalid as anticipated by the '942 patent. Specifically, Teva contends that the '942 patent discloses each limitation of claim 1 of the '830 patent. The parties agree that the '942 patent discloses a "topical ophthalmic pharmaceutical composition." (D.I. 107 at 38; D.I. 112 at 42) In light of the court's construction of "moxifloxacin" *supra*, the court finds that the '942 patent also discloses

"moxifloxacin or a pharmaceutically useful hydrate or salt thereof." In order for Teva to succeed, it must show that the '942 patent discloses the concentration range of 0.1 to 1 wt% and a "pharmaceutically acceptable vehicle."

With respect to the concentration range, the '942 patent states that "[t]he therapeutically active compounds should preferably be present in the abovementioned pharmaceutical formulations in a concentration of about 0.1 to 99.5, preferably about 0.5 to 95% by weight of the total mixture." (PTX 3 at col. 56, ll. 7-10) Teva argues that the disclosed ranges of the '942 patent encompass the 0.1 to 1.0 wt% range claimed in the '830 patent. Teva also alleges the existence of an "inherent range" of 0.1 to 0.5 wt%, resulting from the difference between the low ends of the two explicitly disclosed ranges. Teva asserts that both the explicit and inherent ranges place a person of ordinary skill in the art in possession of the concentration range limitation of claim 1.[26]

A small genus may disclose each species encompassed by that genus, so as to anticipate later claims to the species. *See Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 999 (Fed. Cir. 2006). However, it does not follow that the prior art disclosure of a larger genus necessarily results in the disclosure of every species contained within. *See id.* In *Atofina*, the Court found that the prior art's disclosure of the temperature ranges 150 to 350C and 100 to 500C did not disclose the claimed range of 330 to 450C.

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[26]Teva also offers evidence regarding the composition of CILOXAN® and OCUFLOX® in order to demonstrate the existence of ophthalmic formulations within the claimed concentration range of the '830 patent. Teva essentially argues that this information, combined with the disclosure of the '942 patent, anticipates claim 1 of the '830 patent. Anticipation, unlike obviousness under § 103, requires a single reference to disclose each and every claim limitation. *See Scripps Clinic & Research Found. v. Genentech, Inc.*, 927 F.2d 1565, 1576 (Fed. Cir. 1991). Thus, the court will confine its analysis under § 102 to the '942 patent, which is the only asserted anticipatory prior art.

See id. at 1000 (explaining that "[g]iven the considerable difference between the claimed range and the range in the prior art, no reasonable fact finder could conclude that the prior art describes the claimed range with sufficient specificity to anticipate this limitation of the claim."). The range disparity in *Atofina* is magnified in the case at bar, the claimed range of the '830 patent a mere fraction of the range disclosed by the '942 patent. The court finds that this "considerable difference" renders the expansive range disclosed by the '942 patent non-anticipatory.

Teva also points to an "inherent range" of 0.1 to 0.5 wt% disclosed in the '942 patent. Certainly, the prior art disclosure of a species will anticipate a genus claim encompassing that species. *See Titanium Metals Corp. v. Banner*, 778 F.2d 775, 782 (Fed. Cir. 1985). Thus, it is axiomatic that a concentration range of 0.1 to 0.5 wt% would anticipate a later claim to a range of 0.1 to 1.0 wt%. The court, however, finds that the '942 patent discloses no such range. Teva has constructed this range in an impermissible attempt to attach significance to the end points of the two explicitly disclosed ranges in the '942 patent. *Atofina*, 441 F.3d at 1000. The disclosure in the '942 patent "is only that of a range, not a specific [concentration] in that range, and the disclosure of a range is no more a disclosure of the end points of the range than it is of each of the intermediate points." *Id.*

The '942 patent also fails to describe the "pharmaceutically acceptable vehicle" of claim 1. Teva argues that the list of "customary excipients" provided by the '942 patent discloses this limitation. (PTX 3 at col. 55, ll. 50-59) Within this list, Teva focuses upon the disclosure of water, which forms a substantial part of ophthalmic solutions. (D.I. 100 at 193) However, ophthalmic compositions require a delicate balance of constituents to

qualify as pharmaceutically acceptable. Indeed, several components may be required to obtain the necessary levels of sterility, stability and toxicity, which water alone cannot provide.[27] (D.I. 101 at 276-277;D.I. 102 at 695-696) Furthermore, the excipients used in ophthalmic applications will differ from those applied to different areas of the body. The '942 patent provides a list of excipients, but lacks guidance as to which excipients are suitable to create a "pharmaceutically acceptable vehicle" for an ophthalmic composition. Therefore, the court finds that the '942 patent fails to disclose a "pharmaceutically suitable vehicle."

Teva has failed to demonstrate, by clear and convincing evidence, that the '942 patent discloses either the concentration range or the "pharmaceutically suitable vehicle" of the '830 patent. In view of the foregoing, the court finds that claim 1 of the '830 patent is not invalid for anticipation.

2. Obviousness

a. Legal standard

"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." 35 U.S.C. § 103(a). Obviousness is a question of law, which depends on several underlying factual inquiries.

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[27]This is made especially evident by the examples of solutions, suspensions and ointments provided in the '830 patent. While water comprises a relatively large percentage by weight in the solution and suspension examples, several other components are necessary to achieve the proper vehicle. (PTX 5 at col. 6, l. 34 - col. 7, l. 23)

Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 407 (2007) (quoting *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966)).

"[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR*, 550 U.S. at 419. Likewise, a defendant asserting obviousness in view of a combination of references has the burden to show, by clear and convincing evidence, that a person of ordinary skill in the relevant field had a reason to combine the elements in the manner claimed. *Id.* at 421-22. The Supreme Court has emphasized the need for courts to value "common sense" over "rigid preventative rules" in determining whether a motivation to combine existed. *Id.* at 422. "[A]ny need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed." *Id.*

In addition to showing that a person of ordinary skill in the art would have had reason to attempt to make the composition or device, or carry out the claimed process, a defendant must also demonstrate by clear and convincing evidence that "such a person would have had a reasonable expectation of success in doing so." *PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342, 1360 (Fed. Cir. 2007).

b. Discussion

According to Teva, the '942 patent, alone or in combination with a variety of prior art references, disclosed all of the limitations of claim 1 of the '830 patent. Teva argues that a motivation to combine exists inasmuch as moxifloxacin would have been "obvious to try" in a topical ophthalmic composition, due to both market pressure and the existence of "a finite number of identified, predictable solutions" to treat ophthalmic infections. (D.I. 107 at 35-36, citing *KSR*, 550 U.S. at 419) Teva further contends that the prior art predicted a topical ophthalmic composition of moxifloxacin HCl because a person of ordinary skill in the art would have reasonably expected it to have desirable antibacterial and pharmacological properties. In contrast, Alcon maintains that, in 1998, the prior art characterized moxifloxacin HCl as an undesirable and unsuitable candidate for a topical ophthalmic composition.

In *KSR*, the Supreme Court stated that "the fact that a combination was obvious to try might show that it was obvious under § 103" in certain circumstances. 550 U.S. at 420. That is,

> [w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense.

Id. Teva asserts that moxifloxacin was "obvious to try" in a topical ophthalmic composition due to both the market pressure faced by Alcon as a result of the impending expiration of the patent on ciprofloxacin and the "finite number of identified, predictable solutions" that could serve to act as a successor drug. In support of this argument, Teva emphasizes that Dr. Stroman left the 1997 ICAAC with "five or six"

candidates, among them moxifloxacin, to test for suitability as ciprofloxacin's replacement. Certainly, if the world of potential successors were limited to five or six compounds, it would be obvious to try each in a topical ophthalmic composition. However, the record indicates anything but a finite number of identified, predictable solutions. Specifically, Teva fails to consider that Dr. Stroman's search spanned years and a number of different conferences in which he likely considered thousands of abstracts. (D.I. 102 at 570-71) Dr. Stroman also indicated that, of the roughly one hundred compounds he managed to actually obtain, a majority were not quinolones. (*Id.* at 641) The numerous compounds considered by Dr. Stroman demonstrate that the universe of successor compounds was not as succinctly identified as Teva contends; indeed, the court finds that the realm of potential solutions included the myriad quinolone and non-quinolone antibacterials alike which had been disclosed by the prior art. The court, therefore, concludes that it was not "obvious to try" moxifloxacin in a topical ophthalmic composition.

Teva argues a separate theory concerning a motivation to combine. Dr. Lloyd Allen, Teva's formulation expert, testified that the substitution of moxifloxacin for the other active ingredients of prior art topical ophthalmic compositions was completely predictable in September 1998. Specifically, Dr. Allen opined that one skilled in the art would have reasonably expected that exchanging ofloxacin, the active ingredient of OCUFLOX®, or ciprofloxacin, the active ingredient of CILOXAN®, for moxifloxacin would result in a topical ophthalmic composition that displayed antibacterial properties. (D.I. 100 at 205-06; D.I. 101 at 221, 222-23) Dr. Allen posited that the motivation to make this substitution came from two discrete sources. According to Dr. Allen, both the

biological activity data contained in the 1997 Bayer ICAAC poster and the pharmacological profile disclosed by the '942 patent would have demonstrated to one skilled in the art that "an ophthalmic formulation containing moxifloxacin HCl would be a pharmaceutical composition with antibacterial properties." (D.I. 107 at 34)

While the court does not disagree with Teva's conclusion that a topical ophthalmic composition of moxifloxacin HCl would predictably possess these characteristics, the court finds that this conclusion provides little insight into a question crucial to the obviousness inquiry; namely, whether the prior art motivated a person of ordinary skill to even **select** moxifloxacin for use in a topical ophthalmic composition. *See generally Takeda Chem. Indus. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1357-62 (Fed. Cir. 2007) (no determination of obviousness where the prior art does not lead one of ordinary skill to select "compound b" as starting point); *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008) (no determination of obviousness where the record indicated that "even if an ordinarily skilled artisan sought an FBPase inhibitor, that person would not have chosen topiramate."). Indeed, without questioning why one of ordinary skill would select moxifloxacin for this particular application, Teva avoids consideration of the prior art that taught away from the selection of moxifloxacin, including the salient commercial and regulatory realities of the drug development process.

The '830 patent provides that the field of treating and preventing ophthalmic infections was concerned with developing "improved compositions . . . based on the use of antibiotics that are more effective than existing antibiotics against key ophthalmic pathogens, and less prone to the development of resistance by those pathogens." (PTX

5 at col. 1, ll. 49-53) One skilled in the art would understand that this disclosure referred to the sight-threatening pathogens *Pseudomonas aeruginosa* and *Staphylococcus aureus* and the standard treatment of such by CILOXAN® and OCUFLOX®. (D.I. 101 at 381-87) A person of ordinary skill in the art would also understand that a resistance problem existed with respect to the treatment of these two key ophthalmic pathogens, and that this issue was critical to the development of a viable new treatment. It was evident in 1998 that any potential ophthalmic treatment which did not improve upon the efficacy and resistance issues would be considered impractical and worthless to one skilled in the art.

As discussed previously, when Dr. Stroman stumbled upon the 1997 Bayer ICAAC poster, the *in vitro* data for BAY 12-8039 indicated that moxifloxacin was eight times less active than ciprofloxacin against *Pseudomonas aeruginosa.* (PTX 1098) According to Dr. George Zhanel, a Professor of Medical Microbiology Infectious Diseases at the University of Manitoba, this eight-fold difference in activity is "hugely significant." (D.I. 103 at 860-61) The significance of this diminished activity arises from the quinolone class resistance problem. The treatment of *Pseudomonas aeruginosa* by a quinolone with less activity than ciprofloxacin would drive resistance to quinolones as a whole if the bacterial strains were not completely eliminated. Thus, even though moxifloxacin was more active than ciprofloxacin against *Staphylococcus aureus*, a person of ordinary skill in the art would have dismissed it in light of its poor activity against *Pseudomonas aeruginosa,* the critical intraocular pathogen.

The uncertain toxicity status of moxifloxacin would have also weighed against its development into a topical ophthalmic treatment. While the toxicity profile of a new

compound is unpredictable, quinolones, as a class, were considered extremely toxic. (D.I. 104 at 931) Dr. Zhanel explained that, as a general rule, "the more powerful the quinolones are at killing bacteria, the more powerful they are at killing people." (D.I. 103 at 897-98) Ciprofloxacin and ofloxacin, the exceptions to this rule, were considered generally safe and exhibited negligible side effects. (*Id.*) Thus, one skilled in the art would only consider viable a treatment that exhibited a similar risk profile, especially in light of the intended prophylactic use.[28]

In 1998, having just finished Phase I of the NDA process, moxifloxacin did not possess this profile. Indeed, as previously mentioned, many quinolones that successfully passed Phase I were later determined to exhibit some form of toxicity.[29] (D.I. 104 at 907-14; PTX 2025) The potential for serious adverse reactions would be unacceptable to one skilled in the art considering prophylactic treatments for low risk procedures.[30] Such apprehension is evident in the existence of several quinolones, for which promising toxicity data was available, that were not pursued as ophthalmic treatments. (D.I. 103 at 911-14) Before developing moxifloxacin into a topical ophthalmic composition, one skilled in the art would wait for further reassurance than could be provided by the successful completion of Phase I.

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[28]Dr. Eduardo Alfonso, an ophthalmologist at the Baskin-Palmer Eye Institute in Miami, explained that the predominant use was prophylactically in cataract and Lasik surgery patients, both of which exhibited a low incidence of infection. (D.I. 102 at 397)

[29]Temafloxacin and trovafloxacin, in particular, were only deemed toxic after the completion of all phases of clinical testing. (PTX 2025)

[30]Dr. Zhanel provided several examples of quinolones that, upon ophthalmic administration, could cause a potentially fatal cardiac toxicity. (D.I. 104 at 934-47)

In conducting the obviousness inquiry, the court must also consider whether the prior art, as a whole, "teaches away" from the claimed invention. *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994). The Federal Circuit has explained that a reference "teaches away" if one skilled in the art, "upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." *Id.* In light of the foregoing reasons, the court concludes that both moxifloxacin's *Pseudomonas aeruginosa* resistance profile data, as well as its uncertain but probable toxicity, teach away from the invention of the '830 patent.

Drawing upon a factual background vaguely similar to the case at bar, Teva argues that the finding of obviousness with respect to the substitution of one quinolone for another in *Daiichi Sankyo Co., Ltd. v. Apotex, Inc.*, 501 F.3d 1254 (Fed. Cir. 2007), mandates that this court reach a similar conclusion. The claims in *Daiichi* were drawn to a method of treating ear infections with a topical composition of ofloxacin. *Id.* In making the determination that the claimed invention was obvious, the Court considered a prior art reference, ignored by the trial court,[31] that taught the successful use of ciprofloxacin in a topical solution to treat middle ear infections. *Id.* at 1258. The reference explained that ciprofloxacin, a gyrase inhibitor, "would definitely have to be suitable for use as eardrops" because it lacked appreciable ototoxicity. *Id.* The Court also relied on the testimony of Apotex's expert that one skilled in the art would understand from the

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[31]The trial court dismissed this teaching because it found that the reference spoke beyond what it had erroneously determined to be the level of ordinary skill in the art. *Id.*

reference that ofloxacin, also a gyrase inhibitor, "would be very likely equally effective as ciprofloxacin [sic] when used topically to treat middle ear infections" and that ofloxacin would likely also display a similar lack of ototoxicity. *Id.* Daiichi's only relevant response[32] to the teachings of this reference consisted of the "conclusory statement that [o]ne cannot extrapolate a safety profile for one antibiotic to another."[33] *Id.* at 1259.

Initially, the court notes that the fact-intensive nature of the obviousness inquiry renders it incompatible with the use of a proxy. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1366 (Fed. Cir. 2007). Thus, a determination of the existence or absence of obviousness must rest upon the factual record of the individual case. *Id.* Regardless of this axiom, the court finds several grounds upon which to distinguish the case at bar from *Daiichi*. Importantly, the record is replete with evidence of the general tendency of quinolones, as a class, to exhibit toxic properties, thus foreclosing any claim that a person of ordinary skill would reasonably expect moxifloxacin to be as safe as ciprofloxacin. Furthermore, no expert testified that one skilled in the art would have considered moxifloxacin as effective as ciprofloxacin in treating and preventing intraocular infections. Finally, considerations unique to the field of ophthalmic treatment and prevention, such as ocular penetration and the nature of intraocular pathogens, are sufficient to create hesitation in reading too many similarities between the case at bar and another which concerned a drug delivery system directed towards the ear.

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[32]Daiichi based most of its arguments upon the trial court's improper determination of the level of ordinary skill in the art. *Id.*

[33]The Court explained that "[t]his unsupported statement cannot refute the detailed testimony of Apotex's expert." *Id.*

The court notes that several secondary considerations of nonobviousness support the conclusion that moxifloxacin was not an obvious active ingredient in a topical ophthalmic composition. The record indicates that when Alcon announced its intent to pursue moxifloxacin as an ophthalmic composition, artisans in the field were "upset" and expressed "dismay" over the investigation of another potential resistance-enhancing quinolone believed to be unsuitable for ophthalmic treatment. (D.I. 101 at 415-16) Such skepticism by experts "constitutes strong evidence of nonobviousness." *Environmental Designs, Ltd. v. Union Oil Co.*, 713 F.2d 693, 698 (Fed. Cir. 1983) (citing *United States v. Adams*, 383 U.S. 39, 52 (1966)). In 1998, it was evident that there existed a long felt need for a compound that could more effectively treat intraocular infections of key pathogens without rapidly developing resistance. Furthermore, it is undisputed that the commercial success of VIGAMOX®, an embodiment of claim 1, has resulted in hundreds of millions of dollars in sales. (D.I. 75 at ¶ 4)

The unexpected properties of the invention are likewise probative of nonobviousness. The Federal Circuit has mandated the consideration of all relevant properties of a compound in the context of the obviousness inquiry. *See Eli Lilly & Co. v. Zenith Goldline Pharms., Inc.*, 471 F.3d 1369, 1378 (Fed. Cir. 2006). When "unexpected" and "significant" differences exist between the properties of the claimed invention and those of the prior art, a finding of nonobviousness may be warranted. *Id.* The court finds that the ocular penetration of the topical ophthalmic solution of claim 1 is both unexpected and significant. The eye is comprised of several layers that work in unison to repel a broad spectrum of substances. (D.I. 102 at 697-705) A compound's effective diffusion into, and subsequent retention by, the eye depends upon a variety of

factors, including, inter alia, molecular weight, lipophilicity and hydrophilicity. (*Id.*) At trial, Dr. Ashim Mitra[34] testified that, in light of these factors and the data available for moxifloxacin in 1998, one skilled in the art would conclude that moxifloxacin would penetrate at a slightly lower rate than ofloxacin. (*Id.* at 710-11) Unpredictably, Alcon's tests upon moxifloxacin compositions revealed a penetration rate greater than two times that of ofloxacin. (D.I. 103 at 729; PTX 1116) Each of the claimed compositions exhibit this enhanced penetration rate throughout the concentration range of claim 1. (PTX 1116; PTX 1119)

In conclusion, the court finds no motivation to combine the teachings of the prior art to result in a topical ophthalmic composition of moxifloxacin. Rather, it is evident that the prior art consistently taught away from the use of moxifloxacin in ophthalmic treatments. Finally, several secondary considerations of nonobviousness demonstrate

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[34]Teva requests that the court exclude Dr. Mitra's testimony and accompanying exhibits (PTXs 364-66 and 1116) with respect to unexpected results for failure to comply with Fed. R. Civ. P. 26(e). During a deposition, Dr. Mitra explained that he had only examined the ocular penetration data for VIGAMOX®. (D.I. 103 at 770) At trial, it was shown that Dr. Mitra had instead examined noncommercial moxifloxacin vehicles. (*Id.*) Teva asserts that this was a material change in testimony because the nature of the vehicle can affect ocular penetration. (*Id.* at 761) Therefore, Teva argues, Alcon had an affirmative burden to supplement Dr. Mitra's expert report, and the failure to do so has resulted in prejudice against Teva.

The court initially notes that nothing material has changed with respect to the substance of Dr. Mitra's opinion, that is, that ophthalmic compositions of moxifloxacin exhibit superior ocular penetration when compared to similar compositions of ciprofloxacin and ofloxacin. Furthermore, Teva's allegation of prejudice is exaggerated. While the vehicle can certainly affect ocular penetration, the use of the same vehicle in all of the analyzed compositions will equalize any additional penetration provided by a given vehicle. Thus, it was harmless error that Dr. Mitra mistakenly believed that he had examined commercially optimized formulations when, in fact, his examination concerned noncommercial but standardized vehicles. (*Id.* at 731-32) The court finds no reason to exclude Dr. Mitra's testimony or exhibits.

that it was not obvious to incorporate moxifloxacin into such a composition. Therefore, the court finds that Teva has failed to adduce clear and convincing evidence that the invention of the '830 patent is obvious.

3. Best mode

a. Legal standard

The best mode requirement of 35 U.S.C. § 112, ¶ 1 states:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and **shall set forth the best mode contemplated by the inventor of carrying out his invention**.

35 U.S.C. § 112 (2002) (emphasis added).

"The purpose of the best mode requirement is to ensure that the public, in exchange for the rights given the inventor under the patent laws, obtains from the inventor a full disclosure of the preferred embodiment of the invention." *Dana Corp. v. IPC Ltd. P'ship*, 860 F.2d 415, 418 (Fed. Cir. 1988). Consequently, the best mode requirement of § 112 "requires an inventor to disclose the best mode contemplated by him, as of the time he executes the application, of carrying out the invention." *Bayer AG & Bayer Corp. v. Schein Pharms., Inc.*, 301 F.3d 1306, 1314 (Fed. Cir. 2002) (citation omitted). "The existence of a best mode is a purely subjective matter depending upon what the inventor actually believed at the time the application was filed." *Id.* Because of this subjectivity, § 112 demands actual disclosure, regardless of whether practicing that mode would be within the knowledge of one of ordinary skill in the art. *Id.* Nevertheless,

the extent of this actual disclosure is limited to the invention as defined by the claims. *Id.* at 1315.

In determining whether an inventor has disclosed the best mode, the Federal Circuit has adopted a two-step inquiry. First, the invention must be defined by construing the claims. *Id.* at 1320 (citing *Northern Telecom Ltd. v. Samsung Elec. Co.*, 215 F.3d 1281, 1286-87 (Fed. Cir. 2000)). The Federal Circuit has noted in this regard that "[d]efinition of the invention 'is a legal exercise, wherein the ordinary principles of claim construction apply.'" *Id.* It has also commented that such definition "is a crucial predicate to the factual portions of the best mode inquiry because it ensures that the finder of fact looks only for preferences pertaining to carrying out the claimed invention." *Id.*

Once the claim analysis is complete, the finder of fact may proceed to the second step and determine whether, at the time of filing the application, the inventor possessed a best mode for practicing the claimed invention. *Id.* at 1320. If the inventor subjectively contemplated a best mode, then the fact-finder must evaluate whether the inventor's disclosure is objectively adequate to enable one of ordinary skill in the art to practice the best mode of the claimed invention. *Id.*

The Federal Circuit further has delineated that "if the best mode for carrying out the claimed invention involves novel subject matter, then an inventor must disclose a method for obtaining that subject matter even if it is unclaimed." *Id.* at 1322 (quoting *Eli Lilly & Co. v. Barr Labs., Inc.*, 251 F.3d 955, 965 (Fed. Cir. 2001)). In other words, when the subject matter is unclaimed, but both novel and essential for carrying out the best mode of the claimed invention, disclosure is required. *Id.* With regard to unclaimed

subject matter unrelated to the properties of the claimed invention, the Federal Circuit has acknowledged that an inventor need not disclose a mode for obtaining it. *Id.* (citing *Eli Lilly*, 251 F.3d at 963)

b. Discussion

As discussed previously, Dr. Stroman handled and analyzed only one form of moxifloxacin - that of moxifloxacin HCl (BAY 12-8039). Teva asserts that moxifloxacin HCl was the only mode known to and contemplated by Dr. Stroman. According to Teva, material differences in solubility, stability and tolerability exist between the salt and betaine forms of moxifloxacin. (D.I. 100 at 143; D.I. 102 at 461) Teva contends, in view of these alleged material differences, that Alcon violated the best mode requirement by failing to disclose moxifloxacin HCl in the '830 patent.

Teva relies upon *Chemcast Corp. v. Arco Industries Corp.*, 913 F.2d 923 (Fed. Cir. 1990), wherein the Federal Circuit explained that a patentee's failure to disclose the only mode contemplated results in a violation of the best mode requirement. The claims at issue in *Chemcast* were drawn to a sealing member, such as a grommet, designed to seal an opening in sheet metal. The patentee failed to disclose "(1) the particular type, (2) the hardness, and (3) the supplier and trade name" of the material used to construct the sealing member, resulting in the lower court holding the patent invalid for failure to satisfy the best mode requirement. *Id.* at 926. In affirming the lower court's finding of invalidity, the *Chemcast* court noted that the patentee had selected the material, which had been custom made for the patentee, because it exhibited a desirable hardness. *Id.* at 929. The *Chemcast* court emphasized that "the only embodiment of the claimed invention known" to the patentee included this specific material. *Id.* The Court noted

that a best mode violation is especially evident "where the inventor has failed to disclose the only mode he ever contemplated . . . ." *Id.* at 930.

As an initial matter, the court disagrees with Teva's assertion that moxifloxacin HCl was Dr. Stroman's preferred embodiment. Unlike the patentee in *Chemcast* who preferred the hardness possessed by the undisclosed material, the undisputed evidence before the court indicates that Dr. Stroman held no such preference for moxifloxacin HCl.[35] This finding is supported by Dr. Stroman's testimony that he was unaware of the existence of the salt form and the corroborating correspondence between Dr. Stroman and Bayer regarding the sample of BAY 12-8039, which repeatedly evinced Dr. Stroman's (incorrect) understanding that BAY 12-8039 was nothing more than moxifloxacin betaine. Dr. Stroman's ignorance with respect to the true nature of BAY 12-8039 is understandable, given the focus of his search. Dr. Stroman based his selection upon considerations of biological activity, an invariable characteristic among the salt and betaine forms of moxifloxacin. Conversely, formulation issues such as enhanced solubility[36] were not examined by Dr. Stroman at the time that Alcon filed the '504 and '506 applications. Dr. Stroman needed only to dissolve the compound into solution form, a feat which both the betaine and salt forms are capable of across the concentration range of claim 1. (D.I. 100 at 143) Thus, it is evident from the record that

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[35]Teva has adduced no evidence showing that Dr. Stroman preferred moxifloxacin HCl over moxifloxacin betaine.

[36]Dr. Taylor testified upon cross by defendants that "HCl salts are known . . . for their solubilities." (D.I. 100 at 143)

Dr. Stroman's preferred mode was simply that of a topical ophthalmic solution containing moxifloxacin; the '830 patent fully discloses this embodiment.

Even assuming, *arguendo*, that Dr. Stroman espoused a preference for moxifloxacin HCl, Teva's asserted best mode violation is deficient because no material difference exists between the betaine and salt forms of moxifloxacin. The Federal Circuit has maintained that only "[p]references . . . [that] have a **material effect** on the properties of the claimed invention must be disclosed." *Bayer AG & Bayer Corp. v. Schein Pharms., Inc.*, 301 F.3d 1306, 1321 (Fed. Cir. 2002) (emphasis added). Teva argues that a solution comprised of moxifloxacin HCl will materially differ from a solution comprised of moxifloxacin betaine in terms of both pH and solubility. Specifically, Teva points to the testimony of Dr. Alfonso, who explained that pH can effect the ophthalmic tolerability of a solution. (D.I. 101 at 461) The pH of a solution, however, can be easily adjusted.[37] (D.I. 103 at 820) Teva also contends that the enhanced solubility of moxifloxacin HCl alleviates formulation concerns present with the betaine form. However, the betaine form still dissolves across the concentration range of claim 1, rendering these formulation concerns negligible. (D.I. 100 at 143) Therefore, the court finds that these differences do not have a material effect on the invention of claim 1.

Consequently, Teva has not produced clear and convincing evidence that Alcon failed to disclose its best mode with respect to the composition of claim 1.

4. Written description

a. Legal standard

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[37]This is known as "buffering" the solution.

35 U.S.C. § 112, ¶ 1 also requires that "[t]he specification shall contain a **written description** of the invention . . . ." *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991) (emphasis added). The written description requirement embodies the basic disclosure function of a patent. In exchange for a limited power of exclusion, the patentee must provide to the public a "meaningful disclosure" of his invention. *See Univ. of Rochester v. G.D. Searle & Co., Inc.*, 358 F.3d 916, 922 (Fed. Cir. 2004). "To satisfy the written description requirement, 'the applicant does not have to utilize any particular form of disclosure to describe the subject matter claimed, but the description must clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed.'" *Carnegie Mellon Univ. v. Hoffmann La Roche Inc.*, 541 F.3d 1115, 1122 (Fed. Cir. 2008) (quoting *In re Alton*, 76 F.3d 1168, 1172 (Fed. Cir. 1996)).

A patentee, however, "can lawfully claim only what he has invented and described, and if he claims more his patent is void." *O'Reilly v. Morse*, 56 U.S. 62, 121 (U.S. 1854). Indeed, "a broad claim is invalid when the entirety of the specification clearly indicates that the invention is of a much narrower scope." *Cooper Cameron Corp. v. Kvaerner Oilfield Prods.*, 291 F.3d 1317, 1323 (Fed. Cir. 2002) (explaining *Gentry Gallery v. Berkline Corp.*, 134 F.3d 1473 (Fed. Cir. 1998)). Satisfaction of the written description requirement is a fact-based inquiry, depending on "the nature of the claimed invention and the knowledge of one skilled in the art at the time an invention is made and a patent application is filed." *Carnegie*, 541 F.3d at 1122.

b. Discussion

Teva asserts that claim 1 is invalid because it is directed to a composition in which a preservative is not required. According to Teva, because the specification of the

'830 patent requires the ophthalmic compositions to include a preservative, the invention of claim 1 is not sufficiently described within the meaning of 35 U.S.C. § 112, ¶ 1. Alcon responds that the specification does not require a preservative for all of the embodiments disclosed, and cites to specific examples in which preservatives are absent. Alcon contends that claim 1, therefore, is not broader than the scope afforded to it by the disclosure of the '830 patent.

The court agrees with Alcon that the disclosure of the '830 patent adequately supports a claim that does not include a separate preservative as a limitation. The '830 patent provides, in relevant part, that "[o]phthalmic . . . products are typically packaged in multidose form. Preservatives are thus required to prevent microbial contamination during use." (PTX 5 at col. 5, l. 66-col 6, l. 9) Teva's reliance on this language to establish the necessity of a preservative is misplaced. A person of ordinary skill would interpret the quoted language to indicate that the present invention includes both multidose and single dose forms. (D.I. 101 at 311-12, 435-38, 456-57) Likewise, one skilled in the art would not understand the specification to indicate that a preservative is necessary for a single dose product. (*Id.*) Thus, the specification indicates that preservatives are required, if at all, only for a multidose form of the drug.

It is further evident from the specification that not all of the contemplated embodiments incorporate a preservative. Example 3 of the specification describes an ophthalmic composition lacking a separate preservative. (PTX 5 at col. 7, ll. 1-10) Teva argues that the court should ignore Example 3 because there is no evidence that Alcon ever made this embodiment and there is no evidence that the formulation is self preserving. Teva concludes that the court need not construe claim 1 such that it

includes an inconsistent embodiment. *See Sinorgchem Co. v. ITC*, 511 F.3d 1132, 1136 (Fed. Cir. 2007). Teva misapplies *Sinorgchem*, which addresses the issue of whether a claim may be construed to exclude a specific embodiment; the question at bar is whether the scope of claim 1 is consistent with the disclosure of the specification. *See id.* The court, therefore, finds no reason to exclude Example 3 as instructive of the proper scope of claim 1.

In view of the fact that Alcon has shown two instances in which a preservative is unnecessary, the court finds that Teva has failed to show, by clear and convincing evidence, that the "**entirety** of the specification [of the '830 patent] clearly indicates that the invention is of a much narrower scope." *Cooper*, 291 F.3d at 1323 (emphasis added).

5. Enablement

a. Legal standard

The statutory basis for the enablement requirement, found in 35 U.S.C. § 112, ¶ 1, provides in relevant part:

> The specification shall contain a written description of the invention and of the manner and process of making and using it, in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same.

The Federal Circuit has explained that "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. . . . Tossing out the mere germ of an idea does not constitute enabling disclosure." *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1366 (Fed. Cir. 1997).

To satisfy the enablement requirement, a specification must teach those skilled in the art how to make and to use the full scope of the claimed invention without undue experimentation. *Genentech*, 108 F.3d at 1365. "While every aspect of a generic claim certainly need not have been carried out by the inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention." *Id.* at 1366. The specification need not teach what is well known in the art. *Hybritech v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986).

The use of prophetic examples does not automatically make a patent non-enabling. The burden is on one challenging validity to show, by clear and convincing evidence, that the prophetic examples, together with the other parts of the specification, are not enabling. *Atlas Powder Co. v. E. I. Du Pont de Nemours & Co.*, 750 F.2d 1569, 1577 (Fed. Cir. 1984).

Some experimentation may be necessary in order to practice a claimed invention; the amount of experimentation, however, "must not be unduly extensive." *Id.* at 1576. The test for whether undue experimentation would have been required is not merely quantitative, since a considerable amount of experimentation is permissible if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed. *PPG Indus. Inc. v. Guardian Indus. Corp.*, 75 F.3d 1558, 1564 (Fed. Cir. 1996) (quoting *Ex parte Jackson*, 217 U.S.P.Q. 804, 807 (1982)). A court may consider several factors in determining whether undue experimentation is required to practice a claimed invention,

including: (1) the quantity of experimentation necessary; (2) the amount of direction or guidance disclosed in the patent; (3) the presence or absence of working examples in the patent; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (6) the predictability of the art; and (7) the breadth of the claims. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). These factors are sometimes referred to as the "Wands factors." A court need not consider every one of the Wands factors in its analysis. Rather, a court is only required to consider those factors relevant to the facts of the case. *See Amgen, Inc. v. Chugai Pharm. Co.*, Ltd., 927 F.2d 1200, 1213 (Fed. Cir. 1991).

The enablement requirement is a question of law based on underlying factual inquiries. *Wands*, 858 F.2d at 737. Enablement is determined as of the filing date of the patent application. *In re Brana*, 51 F.3d, 1560, 1567 n.19 (Fed. Cir. 1995).

b. Discussion

Teva alleges two distinct enablement violations. Teva's first contention is premised upon the same theory as its written description argument, namely, the failure of claim 1 to include the preservative mentioned in the specification. Teva argues that this over-claiming also results in an enablement violation. *See In re Mayhew*, 527 F.2d 1229, 1233 (C.C.P.A. 1976). This argument is moot inasmuch as the court has already established that the scope of claim 1 is commensurate with the disclosure provided.

Teva also concludes that a person of ordinary skill cannot practice the full scope of claim 1 without undue experimentation. The court concludes otherwise after application of the Wands factors. With respect to both the amount of experimentation necessary and the amount of guidance disclosed, Teva emphasizes the lack of process

steps for making formulations in the '830 patent. Alcon's experts, however, have demonstrated that one skilled in the art can prepare the compositions of claim 1 without undue experimentation. Dr. Alfonso explained that it would be "routine" and "easy" for the person of ordinary skill to make the formulations of claim 1. (D.I. 102 at 554-56) Teva takes issue with Dr. Alfonso's proposed order of adding ingredients in making the claimed compositions, noting that Dr. Allen would start with water while Dr. Alfonso would add water last. (D.I. 100 at 199-200; D.I. 101 at 448-49) Without making the requisite showing that either procedure would fail, Teva interprets this conflicting evidence as indicating that the '830 patent provides insufficient guidance. This, however, does not account for the very conceivable possibility that multiple procedures may result in the claimed compositions.

The testimony of Dr. Zhanel also demonstrates that the topical ophthalmic compositions can be made without the disclosure of explicit process steps. Dr. Zhanel testified for Alcon that microbiologists likewise have the necessary formulation skills to prepare the compositions of claim 1. (D.I. 104 at 991-93) Dr. Zhanel explained that "a microbiologist, given a recipe, for example, in the '830 patent, could easily make an ophthalmic composition." (*Id.* at 993) In support of this proposition, Dr. Zhanel walked through the steps he would perform to prepare the compositions of claim 1 based only on the list of ingredients provided by the '830 patent. (*Id.* at 994-1004) He further indicated that even his graduate students, who possess less education than the person of ordinary skill, can prepare the claimed compositions. (*Id.* at 992)

Teva contends that Dr. Zhanel's testimony does not aid in determining the degree of experimentation required because his formulations are not pharmaceutically

acceptable and, thus, not within the scope of claim 1. Specifically, Teva seizes upon Dr. Zhanel's testimony that he would not allow solutions prepared by his graduate students into his eyes. (*Id.* at 1004) The court finds it unsurprising that Dr. Zhanel would not allow a solution into his eyes which was not previously proven to be nontoxic. The question, as Alcon correctly identifies, is not whether microbiologists often make pharmaceutical compositions, but rather whether they could do so based on the disclosure of the '830 patent. Dr. Zhanel resolves this issue affirmatively by stating, "I have made compositions to be suitable for the eye. Do I make them frequently? Absolutely not."[38] (*Id.* at 992)

Finally, Teva contends that, while Alcon's experts may have demonstrated how to prepare solutions, no such showing has been made with respect to the gels, ointments and suspensions also covered by claim 1. Teva correctly asserts that claim 1 must be enabled in each of these categories. *See Sitrick v. Dreamworks, LLC*, 516 F.3d 993, 1000 (Fed. Cir. 2008). However, the burden belongs to Teva to demonstrate that the '830 patent fails to enable claim 1; thus, it is of no consequence that Alcon did not first prove that each category covered by claim 1 is enabled. *See Morton Int'l v. Cardinal Chem. Co.*, 5 F.3d 1464, 1470 (Fed. Cir. 1993). Upon review of the record, Teva has

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[38]Alcon asserts that one with even less education than the person of ordinary skill can make the claimed compositions with the guidance provided by the '830 patent. Ms. Kathleen Alford, a microbiologist with a master's degree employed by Alcon, allegedly prepared five compositions within the scope of claim 1 using only the disclosure of the '830 patent. (D.I. 102 at 677-85) Teva contends that this testimony, too, is inapposite to the determination of enablement, because Ms. Alford did not test the resulting composition for pharmaceutical acceptability. (*Id.* at 690) The court agrees with Teva. Because Ms. Alford failed to test for osmolality, tonicity, sterility or activity, her compositions cannot properly be characterized as "pharmaceutically acceptable" and, therefore, do not provide evidence of the enablement of claim 1.

adduced no evidence to support its contention that claim 1 is not enabled. No testimony before the court indicated that the compositions of claim 1 would be difficult or impossible to make. The court, therefore, finds that Teva has failed to show, by clear and convincing evidence, that claim 1 is invalid for lack of enablement.

IV. CONCLUSION

For the reasons discussed above, the court concludes that Alcon has proven, by a preponderance of the evidence, that Teva's ANDA product infringes the '830 patent.

Teva has failed to prove, by clear and convincing evidence, that the '830 is invalid as anticipated, obvious, or for violation of the best mode, written description or enablement requirements of 35 U.S.C. § 112, ¶ 1.

An appropriate order shall issue.

IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

ALCON, INC. and ALCON RESEARCH, LTD.,	)	
Plaintiffs,	)	
v.	)	Civ. No. 06-234-SLR
TEVA PHARMACEUTICALS USA, INC.,	)	
Defendant.	)	

ORDER

At Wilmington, this 19th day of October, 2009, consistent with the memorandum opinion issued this same date;

IT IS ORDERED that:

1. Teva's ANDA product infringes claim 1 of U.S. Patent No. 6,716,830.

2. Teva has failed to prove the invalidity of U.S. Patent No. 6,716,830 by clear and convincing evidence.

3. The Clerk of Court is directed to enter judgment in favor of plaintiffs and against defendant.

United States District Judge