IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

SENJU PHARMACEUTICAL CO. LTD., KYORIN PHARMACEUTICAL CO. LTD. and ALLERGAN, INC.	)	
Plaintiffs,	)	
v.	)	Civ. No. 07-779-SLR
APOTEX INC. and APOTEX CORP.	)	
Defendants.	)	

Jack B. Blumenfeld, Esquire and Maryellen Noreika, Esquire of Morris, Nichols, Arsht & Tunnell LLP, Wilmington, Delaware. Counsel for Plaintiffs. Of Counsel: Richard D. Kelly, Esquire, Stephen G. Baxter, Esquire and Frank J. West, Esquire of Oblon, Spivak, McClelland, Maier & Neustadt, P.C., Alexandria, Virginia.

Francis J. Murphy, Esquire of Murphy & Landon, Wilmington, Delaware. Counsel for Defendants. Of Counsel: David G. Greene, Esquire and Alan B. Clement of Locke Lord Bissell & Liddell LLP, New York, New York, Keith D. Parr, Esquire, Scott B. Feder, Esquire, David B. Abramowitz, Esquire, Patrick C. Gallagher, Esquire and Kevin M. Nelson, Esquire of Locke Lord Bissell & Liddell LLP, Chicago, Illinois.

MEMORANDUM OPINION

Dated: June 14, 2010
Wilmington, Delaware

ROBINSON, District Judge

I. INTRODUCTION

Senju Pharmaceutical Co., Ltd. ("Senju") and Kyorin Pharmaceutical Co., Ltd. ("Kyorin") are co-owners of U.S. Patent No. 6,333,045 ("the '045 patent"). (D.I. 100, ex. 1 at ¶ 1) The '045 patent is directed to aqueous liquid pharmaceutical compositions comprising gatifloxacin and disodium edetate, as well as various methods utilizing these compositions. Allergan, Inc. ("Allergan") holds a New Drug Application ("the NDA"),[1] approved by the United States Food and Drug Administration ("FDA"), which describes a 0.3% gatifloxacin ophthalmic solution containing disodium edetate, sold under the trade name ZYMAR®. (*Id.* at ¶¶ 9, 10) ZYMAR® is indicated for the treatment of bacterial conjunctivitis. (*Id.*) The FDA's Approved Drug Products With Therapeutic Equivalence Evaluations ("the Orange Book") lists, inter alia, the '045 patent and U.S. Patent No. 4,980,470 ("the '470 patent")[2] in connection with ZYMAR®. (*Id.* at ¶¶ 12, 31)

On July 18, 2007, Apotex Inc. filed an Abbreviated New Drug Application ("the ANDA")[3] with the FDA, seeking approval, prior to the expiry of the '045 patent, to manufacture, market and sell a generic version of the 0.3% gatifloxacin ophthalmic solution described in the NDA ("the ANDA product"). (*Id.* at ¶ 13) Apotex Inc.

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[1]NDA No. 02-1493.

[2]The '470 patent, which claims the compound gatifloxacin and its derivatives, expired on December 15, 2009. (*Id.* at ¶ 32) Pediatric exclusivity associated with the '470 patent ends on June 15, 2010, after which time only the '045 patent remains to forestall the emergence of generic aqueous gatifloxacin ophthalmic solutions incorporating disodium edetate as an excipient. (*Id.* at ¶ 51)

[3]ANDA No. 79-084.

subsequently assigned its rights in the ANDA to Apotex Corp. (collectively, "Apotex" or "defendants"). (*Id.* at ¶ 16) On October 17, 2007, defendants sent Senju, Kyorin and Allergan (collectively, "plaintiffs") a notification letter, informing plaintiffs that the ANDA contained a Paragraph IV certification[4] for the '045 patent. (*Id.* at ¶ 17) In the Paragraph IV certification, defendants contend that the ANDA product will not infringe claims 4, 5, 10 and 11 of the '045 patent and that all the claims of the '045 patent are invalid. (*Id.* at ¶ 18)

Plaintiffs brought this infringement action on November 29, 2007 pursuant to 35 U.S.C. § 271(e)(2)(A), alleging that the ANDA product will infringe claims 1-3, 6, 7 and 9 of the '045 patent. (*Id.* at ¶ 19) Defendants responded with affirmative defenses and counterclaims seeking declaratory judgment of noninfringement, invalidity[5] and unenforceability of the '045 patent. (*See* D.I. 63) While defendants maintain that claims 6 and 7 will not be infringed, the parties stipulate that, if valid, the ANDA product will infringe claims 1-3 and 9 of the '045 patent. (D.I. 100, ex. 1 at ¶ 8) The court held a claim construction hearing on December 4, 2009. A bench trial was conducted from January 12-14, 2010, principally to resolve these issues, which have been fully briefed post-trial. (D.I. 110; D.I. 112; D.I. 115; D.I. 116) The court has jurisdiction pursuant to 28 U.S.C. §§ 1331, 1338(a) and 1400(b). 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).

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[4]*See* 21 U.S.C. § 355(j)(2)(A)(vii)(IV).

[5]Defendants include non-asserted claim 8 among these contentions of invalidity.

II. FINDINGS OF FACT

A. The Parties

Senju is a Japanese corporation with its principal place of business in Osaka, Japan. (D.I. 100, ex. 1 at ¶ 1) Senju develops pharmaceutical products that have applications regarding the eye, ear, nose, throat and skin. Kyorin is a corporation organized and existing under the laws of the Nation of Japan, and having its principal place of business in Tokyo, Japan. (*Id.* at ¶ 2) Kyorin engages in the development of pharmaceuticals directed to infectious, immunological, allergic and metabolic diseases. Allergan is a corporation formed under the laws of the State of Delaware, having its principal place of business in Irvine, California. (*Id.* at ¶ 3) The business of Allergan is directed to the development and sale of pharmaceuticals, biologics and medical devices.

Apotex Corp. is a corporation formed under the laws of the State of Delaware, having its principal place of business in Weston, Florida. (*Id.* at ¶ 4) Apotex Inc. is a corporation formed under the laws of the Nation of Canada, having its principal place of business in Ontario, Canada. (*Id.* at ¶ 5) Apotex primarily develops, manufactures and commercializes generic pharmaceutical products.

B. The Asserted Prior Art

1. Gatifloxacin

Fluoroquinolones, otherwise known as quinolone carboxylic acids or simply "quinolones," are a class of broad spectrum antibacterial compounds[6] that share a

[6]Quinolones demonstrate high activity against both gram-negative and gram-positive bacteria. ('470 patent, col. 1:32-35)

common core chemical structure. (*See* DTX 37 at col. 1:7-10; D.I. 107 at 326-28) A carboxylic acid, along with a nitrogen-containing carbon ring and a double-bonded oxygen, are fundamental and common aspects of all quinolone antibiotics. (D.I. 107 at 327-28)

The '470 patent,[7] which was before the examiner during the prosecution of the '045 patent, claims gatifloxacin[8] and its acid derivatives. The properties of this fourth generation quinolone are revealed following a discussion of previously discovered quinolones, to wit, norfloxacin, ofloxacin and ciprofloxacin.[9] (*Id.*, col. 1:32-61) The '470 patent teaches that gatifloxacin represents an improvement over the prior art quinolones in that it exhibits a broader antibacterial activity, higher selective toxicity and safe oral and parenteral administration. (col. 1:62-2:7)

In a passing reference to chemical structure, the '470 patent explains that each of the disclosed quinolones have "similar substituents." (col. 1:41-43) Defendants' expert, Dr. Paul Myrdal ("Dr. Myrdal"), testified that, in this manner, the '470 patent recognizes the structural similarity between gatifloxacin and these prior art quinolones. (D.I. 107 at 326-27) This structural similarity is emphasized in a slide prepared by Dr. Myrdal, wherein the blue portion of the molecules represents a chemical backbone common to all four quinolones and the black portions represent functional group

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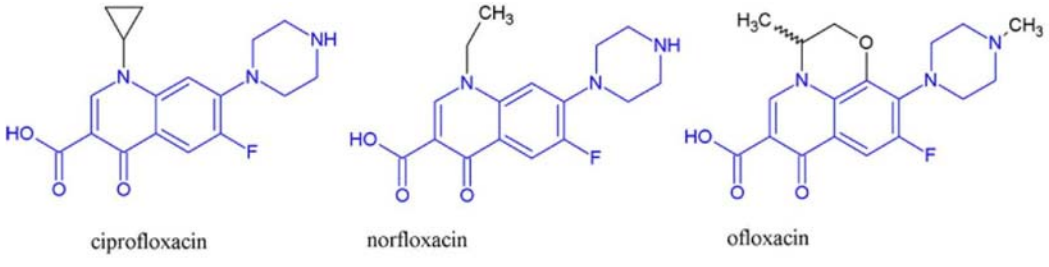
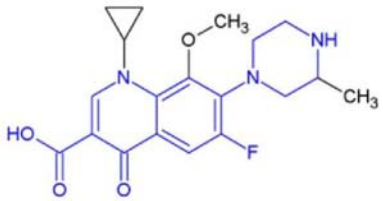
[7]The '470 patent issued to Kyorin in 1990. (D.I. 100, ex. 1 at ¶¶ 21, 22)

[8]The IUPAC, or systematic, name for gatifloxacin is 1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7(3-methyl-1-piperazinyl)-4-oxo-3-quinoline carboxylic acid.

[9]Ofloxacin and ciprofloxacin are both third generation quinolones, and norfloxacin is a second generation quinolone. (D.I. 106 at 44-45)

variations:





(DTX 194 at 44) Dr. Myrdal further testified that gatifloxacin is a polar compound due to its ability to readily ionize and because it contains several polar moieties. (D.I. 107 at 343)

2. Disodium edetate

Disodium edetate is the disodium salt of ethylenediamine tetraacetic acid (commonly known as "EDTA").[10] (D.I. 100, ex. 1 at ¶ 40) EDTA, a multi-purpose excipient,[11] is widely known as a chelating agent.[12] (D.I. 107 at 332-33; DTX 166 at

[10]Because the principles of solution chemistry render EDTA and disodium edetate functionally equivalent, and insofar as the parties make no distinguishing arguments on these grounds, the court treats a prior art disclosure of a property of one compound as the disclosure of the property with respect to both, and refers to these compounds interchangeably.

[11]The 1986 Handbook of Pharmaceutical Excipients discloses that EDTA, in addition to its chelating function, may act as an antibacterial synergyst/preservative

109-110) EDTA has four carboxylic acid groups. (D.I. 107 at 354; D.I. 108 at 669) In a September 1967 article by D.E. Griffith ("the Griffith reference"), the author reported that EDTA, by "sequestering" metal ions through a chelating mechanism, prevents coloration in a variety of active pharmaceutical ingredients. (JTX 56 at 1197-98) The Griffith reference teaches that disodium edetate, in concentrations of between 0.005 and 0.02 w/v%, prevented coloration of papaverine hydrochloride and that, in concentrations between 0.005 and 0.04 w/v%, it similarly prevented coloration in other pharmaceutical agents. (*Id.*)

EDTA is also known to increase the corneal permeability of certain polar compounds. (*See* JTX 12) A layer of epithelial cells, bound tightly together by calcium ions, forms a protective barrier that prevents foreign molecules from entering the eye. (*Id.* at 111) In a 1985 publication by Grass et al. ("the Grass reference"), considered during the prosecution of the '045 patent, the authors sought to determine the effect of EDTA on the permeability of organic and inorganic compounds with respect to the corneal epithelia.[13] (*Id.* at 110) The Grass reference teaches that EDTA can reduce the number of calcium ions through chelation, thus creating small channels between

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enhancer. (DTX 166 at 6)

[12]A chelating agent can complex with certain undesirable ions (generally metals), thereby removing them from solution. (D.I. 107 at 332-333) This chelating effect is achieved in EDTA through its four carboxylic acid groups which act to wrap around these ions, forming complex bonds with - and thereby inactivating within the solution - the targeted ions. (D.I. 107 at 354; D.I. 108 at 669)

[13]The authors note that "the effects of chelating agents such as EDTA on the permeability of inorganic and organic solutes have been well documented in other epithelia, as well as the corneal endothelium, [but] no definitive studies examining the effects of these compounds upon the corneal epithelia have been reported." (*Id.*)

corneal epithelial cells. (*See id.*) These channels allow polar molecules to penetrate through the cornea into the aqueous humor of the eye. (*See id.*) In reporting the results of this study, the Grass reference describes how the addition of 0.5 w/v% disodium edetate to separate solutions of glycerol and cromolyn resulted in increased corneal permeability in both solutions. (*Id.* at 112) A lower unspecified concentration of EDTA was also shown to function in this manner, albeit to a lesser extent.[14] (*Id.*) The authors of the Grass reference conclude that the propensity of EDTA to increase the corneal permeability of polar compounds has a "direct bearing upon ophthalmic solutions currently in use."[15] (D.I. 107 at 341; *see also* JTX 12 at 112-13)

3. Aqueous quinolone ophthalmic compositions comprising disodium edetate

Dr. Myrdal testified at trial that, in the context of quinolone solution chemistry, the variations in functional groups among the quinolones named by the '470 patent, shown in black, *supra*, are "really not from a physical/chemical standpoint huge differences." (D.I. 107 at 326-27) Generally, he contends that, while different functional groups may result in some differences in solubility (*id.* at 399-402), one of skill in the art can expect a relatively predictable pH-dependent solubility profile for these quinolones. (*Id.* at 329-30, 350-53) In support of this opinion, Dr. Myrdal relies upon a 1989 article by Riley et

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[14]In one example, the authors inhibited the corneal permeability of a solution of glycerol and 0.5 w/v% EDTA by adding calcium to the solution. This calcium complexes with the EDTA, leaving less EDTA to interact with the calcium ions in the corneal epithelia.

[15]Glycerol is a small polar compound, while cromolyn is a large pharmaceutically active polar compound. (JTX 12 at 112; see also D.I. 107 at 341-42)

al. ("the Riley reference"),[16] which proposed several simulated solubility profiles for quinolones. (D.I. 108 at 665; JTX 15) The Riley reference demonstrates that quinolones with similar pK_a values exhibit a U-shaped solubility curve with an inflection point around each of the pK_a values.[17] (*See* JTX 15 at 32-34) A further teaching of the Riley reference describes how the addition of carboxylic acids of various sizes and structures to a quinolone solution maintained at pH 5 resulted in an increased solubility of the quinolone. (*Id.*)

U.S. Patent No. 4,551,456 ("the '456 patent"), which issued in 1985, teaches that then-known quinolones[18] are both "compatible with ocular tissue" and useful in treating bacterial ocular infections through topical administration. ('456 patent at col. 1:13-17) One of two exemplary ophthalmic compositions disclosed by the '456 patent comprises an aqueous solution of 0.3 w/v% norfloxacin and 0.01 w/v% disodium edetate. The '456 patent discloses EDTA in a list of 8 excipients described as "conventional ingredient[s]" in ophthalmic compositions. (*Id.* at col. 2:5-10)

U.S. Patent No. 4,780,465 ("the '465 patent"), which discloses aqueous compositions for the quinolone lomefloxacin, likewise characterizes disodium edetate as a conventional excipient. (col. 2:31-46) The '465 patent addressed the low solubility

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[16]Plaintiffs' expert, Dr. Valentino Stella ("Dr. Stella"), co-authored this paper. (D.I. 108 at 664)

[17]In solution chemistry, pK_a represents the logarithmic measure of the strength of an acid in solution, i.e., the tendency of a compound to accept or donate a proton. A numerically higher pK_a corresponds to a compound that is more basic and less acidic.

[18]The quinolones discussed by the '456 patent include norfloxacin, ofloxacin, perfloxacin, enoxacin and ciprofloxacin. (*Id.* at col.1:30-36)

exhibited by lomefloxacin solutions containing sodium chloride, another common eye drop excipient. (col. 3:7-20) The inventors of the '465 patent solved these solubility issues irrespective of the presence of disodium edetate in the composition. Two exemplary ophthalmic compositions described in the '465 patent, similar to the ophthalmic composition disclosed by the '456 patent, contain 0.3 w/v% lomefloxacin and 0.01 w/v% disodium edetate. (col. 4:1-23)

Consistent with the '456 patent, the '470 patent discloses that pharmaceutical formulations of gatifloxacin follow "the routes well known . . . " with respect to "oral[] and parenteral[]" administration, including " . . . liquids [and] eye drops . . . ." ('470 patent at col. 7:21-26) While the '470 patent does not provide any guidance regarding these formulations, the 1995 Physician's Desk Reference ("the PDR") provides several example formulations of then-available quinolone ophthalmic solutions. (*See* DTX 159) According to the PDR, the commercially marketed eye drop formulation of ciprofloxacin, CILOXAN®, contained 0.05 w/v% disodium edetate. (*Id.* at 472) Although in an unspecified amount, the marketed formulation of norfloxacin (CHIBROXIN®) likewise contained disodium edetate. (*Id.* at 1508) A third listed formulation, ofloxacin (OCUFLOX®), does not contain disodium edetate. (*Id.* at 496)

C. The Invention and Prosecution of the '045 patent

Shinichi Yasueda ("Yasueda"), a Senju employee of fifteen years, began experimenting with solutions of gatifloxacin after Kyorin licensed the '470 patent to Senju. (D.I. 106 at 65) Multiple research reports ("the research reports") authored by Yasueda demonstrate that the addition of EDTA to an aqueous gatifloxacin solution

both increases the corneal permeability and prevents the precipitation of gatifloxacin. (JTX 23; JTX 24; JTX 25; JTX 30; JTX 31)

Several studies in the research reports form the basis for Yasueda's conclusion presented in experiment 1 of the '045 patent, which states that the corneal permeability of gatifloxacin increased "by about 1.2 and 1.5 times" in the presence of EDTA. ('045 patent at col. 4:1-5) The first study, which appears in table 7 of the research reports, presented the testing results[19] of two formulations disclosed by table 1 of the '045 patent: formulation B (gatifloxacin alone)[20] and formulation C (gatifloxacin with disodium edetate).[21] (JTX 24 at 11; D.I. 106 at 85) table 7 is based on a sample size of three eyes for formulation B and five eyes for formulation C. (D.I. 106 at 86) A second study, also concerning formulations B and C, is reported in table 9 of the research reports. (JTX 24 at 12) In this study, Yasueda compared the aqueous humor migration of gatifloxacin and levofloxacin and concluded that the aqueous humor migration was "virtually the same" for these two compounds. Yasueda did not disclose either the sample size or his conclusion about the relative aqueous humor migration of gatifloxacin and levofloxacin.

The '045 patent does disclose that the area under the curve ("AUC") data

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[19]To measure corneal permeability, the subject formulation is instilled into the eyes of one or more male Japanese albino rabbits. At a designated time after this instillation, the rabbits are sacrificed and the eyes are harvested. The aqueous humor is then collected from each eye, and the concentration of the formulation is measured. (*See* '045 patent at col. 3:44-49)

[20]Formulation B corresponds to F-1 in the research reports.

[21]Formulation C corresponds to E-4 in the research reports.

presented by table 10 demonstrated that formulation C exhibited a corneal permeability 1.46 times greater than formulation B. (JTX 24 at 12) Yasueda also revealed several comparison tests which showed that a solution of gatifloxacin and EDTA demonstrated approximately 1.2 times the corneal permeability of its non-EDTA counterpart at the one hour mark. (JTX 25; JTX 30; JTX 31)

Yasueda also presented several precipitation studies which are summarized in experiment 2 of the '045 patent. (*See* JTX 23) Experiment 2 presents the data that supports Yasueda's conclusion that the precipitation of gatifloxacin "is prevented by formulating disodium edtate in an aqueous liquid preparation of gatifloxacin." ('045 patent at col. 4:51-54) Formulation D[22] and formulation C, both of which comprised, inter alia, gatifloxacin, disodium edetate and sodium chloride, did not exhibit precipitation after ten freeze-thaw cycles. (*Id.* at 8) The research reports also contained the results of two formulations, formulations E-1 and E-3, which lacked sodium chloride and eventually precipitated after multiple freeze-thaw cycles. (*Id.*) Likewise, this same study revealed that several formulations without EDTA did not precipitate after 10 freeze-thaw cycles. (*Id.*) Yasueda did not disclose the results regarding either formulations E-1 and E-3 or those formulations without EDTA which did not precipitate.

On December 25, 2001, the '045 patent, entitled "Aqueous Liquid Pharmaceutical Composition Comprised of Gatifloxacin," was issued listing Yasueda and Katsuhiro Inada ("Inada") as inventors and Senju and Kyorin as assignees. (D.I.

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[22]Formulation D corresponds to formulation E-2 in the research reports.

100, ex. 1 at ¶ 6) The '045 patent contains eleven claims. Only claims 1-3 and 6-9 are at issue in this case. They read as follows:

> 1. An aqueous liquid pharmaceutical composition which comprises gatifloxacin or its salt and disodium edetate.
>
> 2. The aqueous liquid pharmaceutical composition according to claim 1, wherein pH of the composition is within the range of 5 to 8.
>
> 3. The aqueous liquid pharmaceutical composition according to claim 1, where the composition is in the form of eye drops.
>
> 6. A method for raising corneal permeability of gatifloxacin which comprises incorporating disodium edetate into eye drops containing gatifloxacin or its salt.
>
> 7. A method for preventing precipitation of gatifloxacin crystals which comprises incorporating disodium edetate into an aqueous liquid preparation containing gatifloxacin or its salt.
>
> 8. A method for preventing coloration of gatifloxacin which comprises incorporating disodium edetate into an aqueous liquid preparation containing gatifloxacin or its salt.
>
> 9. The aqueous liquid pharmaceutical composition according to claim 2, where the composition is in the form of eye drops.

D. The ANDA

On July 18, 2007, defendants filed two ANDA applications with the FDA seeking approval to manufacture and sell generic 0.3 w/v% gatifloxacin ophthalmic solutions. (D.I. 100, ex. 1 at ¶ 13) The ANDA currently at issue is directed to a 0.3 w/v% gatifloxacin solution containing 0.1 w/v% disodium edetate. (PTX 139) Defendants also filed a second ANDA[23] directed to a 0.3 w/v% gatifloxacin ophthalmic solution which did not contain disodium edetate ("the second ANDA"). (D.I. 100, ex. 1 at ¶ 14) The FDA informed defendants that, due to the absence of disodium edetate, the

[23]ANDA No. 79-083.

second ANDA would not be accepted for filing. (D.I. 100, ex. 1 at ¶ 15)

The gatifloxacin used to prepare the ANDA product is known as gatifloxacin hemihydrate. (PTX 139 at 210734) Each molecule of gatifloxacin in a gatifloxacin hemihydrate crystal is bound to 0.5 molecules of water. (*Id.*) By constrast, ZYMAR® is formulated using gatifloxacin sesquihydrate. (*Id.* at 210657) In a gatifloxacin sesquihydrate crystal, each molecule of gatifloxacin is bound to 1.5 molecules of water. (*Id.*) Once dissolved in an aqueous solution, the water bound to these respective forms is released into the solution, and both gatifloxacin hemihydrate and gatifloxacin sesquihydrate become functionally equivalent. (D.I. 107 at 257-59)

Defendants use hydrochloric acid and sodium hydroxide to adjust the pH of the ANDA product. This reaction generates excess sodium chloride, such that the 8.2 mg/mL sodium chloride originally added to the solution increases to 8.6 mg/mL, the amount of sodium chloride contained in ZYMAR®. (D.I. 107 at 259-62) An identical osmolarity[24] reinforces the understanding that both ZYMAR® and the ANDA product contain the same ultimate concentration of sodium chloride. (PTX 139 at 211019; D.I. 107 at 263-64, 437-38)

Defendants confirm the equivalence of the ANDA product, noting that "[t]here are no differences between our proposed formulation and that of [ZYMAR®]. As indicated in the Product Development Report[,] the proposed formulation is a solution that is

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[24]Osmolarity reflects the number of osmoles of solute per unit volume of solution. Osmolarity differs from molarity in that osmolarity measures particles of solute rather than moles of solute, the distinction being that not all solute will dissociate in solution. Defendants have conceded that only sodium chloride, a salt that freely dissociates in solution, affects this measurement in the ANDA product. (D.I. 107 at 219)

equivalent to [ZYMAR®] both quantitatively and qualitatively. As there is no difference between the two formulations, no potential concerns are expected with respect to therapeutic equivalence." (PTX 139 at 210693)

III. CONCLUSIONS OF LAW

A. Infringement

1. Legal standard

"'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). Because a claim of infringement predicated upon the filing of an ANDA concerns prospective events, the court must consider "[w]hat is likely to be sold, or, preferably, what will be sold, [to] ultimately determine whether infringement exists." *Glaxo Inc. v. Novopharm Ltd.*, 110 F.3d 1562, 1570 (Fed. Cir. 1997).

"Direct infringement requires a party to perform each and every step or element

of a claimed method or product." *BMC Res., Inc. v. Paymentech, L.P.*, 498 F.3d 1373, 1378 (Fed. Cir. 2007). "If any claim limitation is absent from the accused device, there is no literal infringement as a matter of law." *Bayer AG v. Elan Pharm. Research Corp.*, 212 F.3d 1241, 1247 (Fed. Cir. 2000).

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).

2. Discussion

Defendants have stipulated that, if found valid, the ANDA product infringes claims 1-3 and 9 of the '045 patent. (D.I. 100, ex. 1 at ¶ 8) In furtherance of the contention that the ANDA product also infringes claims 6 and 7, plaintiffs proffer several pre-litigation studies, including the results of several studies submitted to the FDA to support the NDA. Defendants do not dispute that the ANDA product contains disodium edetate in an amount of 0.001 to 0.2 w/v% as required by the court's construction of claims 6 and 7. Rather, the dispositive issue before the court concerns the limitations contained in the preambles of these claims, namely, whether the disodium edetate contained in the ANDA product increases the corneal permeability and prevents the precipitation of gatifloxacin. Despite admitting in the ANDA that there are no differences between the ANDA product and ZYMAR®, defendants contend that plaintiffs rely on flawed circumstantial evidence and take issue with the alleged failure to test exactly the formulation described in the ANDA. Also submitted for the court's consideration is testing commissioned by defendants that allegedly demonstrates the

noninfringement of the ANDA product. The court evaluates, then, the sufficiency of plaintiffs' evidence on infringement within the context of each claim.

a. Claim 6

The court has concluded that the preamble "raising corneal permeability of gatifloxacin" further limits claim 6 and is properly construed to mean "showing an increased concentration of gatifloxacin in the aqueous humor." Plaintiffs submit that both testing by Senju ("the Senju studies") and by Allergan ("the Allergan studies") demonstrate that disodium edetate increases the corneal permeability of gatifloxacin in the ANDA product.

The Senju studies, preformed prior to the filing of the ANDA, compared the corneal permeability of a 0.3 w/v% gatifloxacin eye drop solution with another solution identical but for the additional inclusion of EDTA. (JTX 30; JTX 31) The results of these studies demonstrated that the gatifloxacin concentrations in the aqueous humor were significantly higher in the solution containing EDTA. (D.I. 106 at 97-98, 246-48; D.I. 107 at 249-50) Defendants provide several allegations as to why this evidence cannot demonstrate that the ANDA product infringes claim 6.

First, defendants contend that plaintiffs failed to proffer critical evidence of how the formulations would behave *in vivo*. The alleged impropriety of plaintiffs' testing method, which involved the harvesting of the eyes of male Japanese albino rabbits as described above, is, according to defendants, implicit in the "many differences between rabbit eyes and human eyes that could affect corneal permeability . . . ." (D.I. 110) The evidence of record establishes that the use of rabbit eye and cell cultures to investigate corneal permeability is not only standard practice, but the only acceptable way of doing

so. (D.I. 107 at 252-53) Indeed, obvious ethical concerns counsel against defendants' suggestion of human testing. Notwithstanding defendants' contrarian position, the study commissioned by defendants to convince the FDA that EDTA was not required to establish the bioequivalence of the ANDA product to ZYMAR® ("the NucroTechnics study") relied upon the use of rabbit eyes models. (JTX 33 at 14040-41) The court concludes that it was appropriate for plaintiffs to use rabbit eye models to determine if EDTA increases the corneal permeability of gatifloxacin within the meaning of claim 6.

Defendants also argue that, in contrast to the ANDA product, the formulations in the Senju studies did not contain benzalkonium chloride ("BAK"). (*See id.*) This results in a material difference, according to defendants, because BAK is a known corneal permeability enhancer. However, the Allergan studies, discussed *infra*, demonstrated that BAK did not affect corneal permeability in ZYMAR®, which contains the same amount of BAK as the ANDA product. (JTX 24; D.I. 106 at 69-70; D.I. 107 at 249) "A patentee may prove infringement by any method of analysis that is probative of the fact of infringement, and circumstantial evidence may be sufficient." *Martek Biosciences Corp. v. Nutrinova, Inc.*, 579 F.3d 1363, 1372 (Fed. Cir. 2009). The court finds that the Senju studies are probative and concludes that it is appropriate for the purposes of infringement to equate the ANDA product with the 0.3 w/v% gatifloxacin solution containing disodium edetate from the Senju studies.

Plaintiffs also proffer the results of the Allergan studies, which involved the comparison of ZYMAR® with 0.3 w/v% and 0.5 w/v% gatifloxacin solutions which did not contain EDTA. These formulations were tested *in vitro* using cultured rabbit cornea epithelial cells and revealed that ZYMAR® had corneal penetration values nearly three

times higher than the solutions lacking EDTA. (PTX 88; D.I. 106 at 203; D.I. 107 at 251-53) Defendants object to the Allergan studies because the formulations without EDTA contained a salt buffer and ZYMAR® contained BAK. (D.I. 107 at 211-13) Dr. Stella testified at trial that neither of these distinctions altered his opinion that EDTA caused an increase in the concentration of gatifloxacin in the aqueous humor. (D.I. 107 at 251-53) Consequently, to the extent that there are no material differences between the formulation of ZYMAR® and that of the ANDA product, the court concludes that the Allergan studies are likewise probative of infringement. *Martek*, 579 F.3d at 1372.

Defendants allege that the NucroTechnics study provides the only meaningful insight to the infringement inquiry, as it is the only study which specifically considered the ANDA product. (*See* JTX 33; *see also* PTX 140) According to defendants, the NucroTechnics study demonstrates that EDTA has no effect upon the corneal permeability of gatifloxacin. The NucroTechnics study was designed both to convince the FDA that EDTA has no effect upon the corneal permeability of gatifloxacin and to "invalidate the ['045] patent." (PTX 85 at 201000; PTX 130 at 17008) The FDA, however, rejected the second ANDA despite the NucroTechnics study. (PTX 156)

With respect to defendants' complaint that plaintiffs failed to provide evidence of testing of the ANDA product, the court is satisfied that plaintiffs tested the product that defendants were likely to market as described in the ANDA. *See Glaxo*, 110 F.3d at 1570. Moreover, insofar as the goal of the NucroTechnics study was to demonstrate the similarity of the aqueous humor concentrations of gatifloxacin in the ANDA product and the formulations without EDTA, at a minimum, the court questions the objectivity of this study as evidence of noninfringement. The record also demonstrates that this

study was not fully vetted by the discovery process as plaintiffs were denied the ability to depose anyone who actually preformed the study.[25] Accordingly, the court declines to accord the NucroTechnics study with the same evidentiary merit as plaintiffs' pre-litigation studies that have been subjected to the full discovery process.

Upon weighing the evidence proffered by the parties, the court concludes that plaintiffs have demonstrated, by a preponderance of the evidence, that the ANDA product infringes claim 6 of the '045 patent, i.e., that it incorporates the claimed concentration of 0.01 w/v% disodium edetate in a manner that increases the aqueous humor concentration of gatifloxacin.

b. Claim 7

Plaintiffs contend that the ANDA product infringes the method of claim 7. As construed, this method requires the use of 0.001 to 0.2 w/v% disodium edetate to inhibit the precipitation of gatifloxacin in an aqueous gatifloxacin solution. Plaintiffs support this contention with a study conducted by Cyanta Analytical Laboratories ("the Cyanta study"), which concerned a freeze-thaw comparison of a product prepared according to the ANDA and another identical preparation lacking EDTA. (PTX 163 at 350; D.I. 106 at 111-126) Dr. Jonathan Mahnken ("Dr. Mahnken"), plaintiffs' statistical expert, analyzed the Cyanta study and concluded that it demonstrated "a reduced rate of precipitation and a delayed onset of precipitation" for the formulations containing EDTA. (PTX 188; D.I. 106 at 146-164)

Defendants offer multiple criticisms of the Cyanta study. First, defendants note

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[25]The results of the NucroTechnics study were interpreted by defendants' experts. (D.I. 107 at 390, 443-45, 491-92)

that the Cyanta study used a formulation incorporating gatifloxacin sesquihydrate instead of the gatifloxacin hemihydrate defendants provided to plaintiffs. (D.I. 106 at 129) As explained above, these materials are functionally equivalent once in solution. Defendants also contend that the Cyanta study did not account for the formulation's final pH, a key factor in whether gatifloxacin precipitates. Dr. Myrdal conceded at trial, however, that the Cyanta study carried out the pH measurements and final dilution step in the same manner as described in the ANDA. (D.I. 107 at 439-40) Finally, defendants contend that when a precipitate was observed in the Cyanta study, the composition of the precipitate was not conclusively identified and, thus, cannot be offered as evidence of the precipitation of gatifloxacin. This position is refuted by the mass spectral analysis preformed during this study, which identified the precipitate as gatifloxacin. (PTX 169) Moreover, the parties do not dispute that gatifloxacin is the only solute present in sufficient quantities to precipitate. (D.I. 107 at 264-66)

In rebuttal of the evidence presented by the Cyanta study, defendants proffer the results of an internal freeze-thaw testing. Defendants allege that this freeze-thaw testing demonstrates that neither the ANDA product nor an otherwise identical solution without EDTA precipitated. (PTX 4; PTX 20; D.I. 107 at 396) Using a different protocol than that described by the '045 patent, the thawing stage of defendants' method brought samples to 40 °C (104 °F), a temperature at which many precipitates would re-dissolve. (D.I. 107 at 442) Defendants do not dispute that precipitation is temperature dependant. (*Id.*)

In view of the foregoing, the court concludes that plaintiffs have demonstrated, by a preponderance of the evidence, that the ANDA product infringes claim 7 of the

'045 patent, namely, that it incorporates the claimed concentration of 0.01 w/v% disodium edetate in a manner that will inhibit or hinder the precipitation of gatifloxacin from an aqueous gatifloxacin solution.

B. Obviousness

1. 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.

> 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, 406 (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 418. Likewise, a defendant asserting obviousness in view of a combination of references has the burden to show that a person of ordinary skill in the relevant field had a reason to combine the elements in the manner claimed. *Id.* at 418-19. 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 419-20. "[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.* at 420. 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 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).

"Because patents are presumed to be valid, *see* 35 U.S.C. § 282, an alleged infringer seeking to invalidate a patent on obviousness grounds must establish its obviousness by facts supported by clear and convincing evidence." *Kao Corp. v. Unilever U.S., Inc.*, 441 F.3d 963, 968 (Fed. Cir. 2006) (citation omitted). In conjunction with this burden, the Federal Circuit has explained that,

> [w]hen no prior art other than that which was considered by the PTO examiner is relied on by the attacker, he has the added burden of overcoming the deference that is due to a qualified government agency presumed to have properly done its job, which includes one or more examiners who are assumed to have some expertise in interpreting the references and to be familiar from their work with the level of skill in the art and whose duty it is to issue only valid patents.

PowerOasis, Inc. v. T-Mobile USA, Inc., 522 F.3d 1299, 1304 (Fed. Cir. 2008) (quoting *Am. Hoist & Derrick Co. v. Sowa & Sons*, 725 F.2d 1350, 1359 (Fed. Cir. 1984)).

2. Discussion

a. Claims 1-3 and 9

As the asserted prior art does not explicitly disclose both gatifloxacin and EDTA in the same reference, defendants contend that the prior art abounds with reasons to

combine these two compounds to arrive at the aqueous ophthalmic composition of the '045 patent.[26] Specifically, defendants point to the '456 patent, which teaches that disodium edetate is a conventional excipient that can be used in topical ophthalmic aqueous quinolone compositions. The '456 patent also discloses an exemplary formulation of a 0.3% quinolone solution that incorporates 0.01 w/v% disodium edetate - an amount explicitly within the range of concentrations claimed by the '045 patent as construed by this court. According to the '470 patent, the quinolones disclosed by the '456 patent are structurally similar to gatifloxacin. In summation, defendants argue that, insofar as the '470 patent teaches that gatifloxacin may be formulated in a manner similar to previously known and structurally similar quinolone compositions - including those compositions intended for ophthalmic administration - it would be obvious to look to the '456 patent for formulation guidance and arrive at an aqueous gatifloxacin composition containing disodium edetate in an amount of 0.001 to 0.2 w/v% as claimed by the '045 patent.

Plaintiffs vigorously contest this portrayal of the prior art, arguing that Dr. Stella did not uncover any publications or theories regarding the ability of EDTA to affect the corneal permeability or precipitation of any quinolone drug composition, let alone a gatifloxacin composition, prior to the invention of the '045 patent. According to plaintiffs, even when a reference describes EDTA as a quinolone-compatible excipient,

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[26]Despite requesting a construction of "disodium edetate" that would confine this limitation to a specific range of concentrations, i.e., 0.001 to 0.2 w/v%, plaintiffs make no prior art distinction based on this construction or any of the limitations contained in dependent claims 2 (pH between 5 and 8), 3 (eye drops), and 9 (eye drops with pH between 5 and 8).

the disclosure suffers from a lack of guidance while simultaneously placing EDTA alongside "a laundry list" of such excipients. (D.I. 112 at 26)

In this regard, consistent with the court's construction, the invention of independent claim 1 is an aqueous liquid pharmaceutical composition comprising gatifloxacin or its salt and 0.001 to 0.2 w/v% disodium edetate. Dependent claim 2 limits this composition to a pH between 5 and 8, a condition that renders the composition suitable for topical ophthalmic administration. Dependent claim 3 limits the composition of claim 1 to eye drops. Claim 9 depends from claim 2 and further limits this composition to eye drops. Notably, neither corneal permeability nor precipitation behavior forms the substance of any of these limitations.

Moreover, the court declines to accept the characterization of the prior art disclosure of EDTA as among a "laundry list" of excipients compatible with quinolones. (D.I. 112 at 26; D.I. 116 at 8, 15) The Federal Circuit has predicated a finding of nonobviousness on a sheer number of variable combinations; however, the Court did so in the face of a prior art disclosure of a "potentially infinite genus." *In re Baird*, 16 F.3d 380, 382 (Fed. Cir. 1994) (quoting *In re Jones*, 958 F.2d 347, 350 (Fed. Cir. 1992)). The case at bar does not remotely approach an infinite genus, as disodium edetate is listed among eight "conventional ingredients" in the '456 patent and a similarly small group of excipients in the '465 patent. ('456 patent at col. 2:1-16; '465 patent at col. 2:36-49)

Plaintiffs also argue that the prior art demonstrates the unpredictability of quinolone solutions, again emphasizing the absence of any teaching that disodium edetate is desirable. Highlighting the difficulties presented by the '465 patent in

formulating an aqueous solution of lomefloxacin with a few conventional tonicity agents (sodium chloride and potassium chloride), plaintiffs suggest that one skilled in the art would predict gatifloxacin to display similar incompatibilities, perhaps with a different conventional excipient such as disodium edetate. (D.I. 112 at 26) However, the very reference relied upon to establish the general unpredictability of quinolone/excipient combinations includes an example formulation comprising lomefloxacin and disodium edetate. ('465 patent at col. 2:31-46)

The prior art characterizes gatifloxacin as nontoxic and superior in terms of antimicrobial activity, but structurally similar to its prior art quinolone counterparts. One skilled in the art[27] would understand that compositions of gatifloxacin follow "the routes well known . . . " with respect to "oral[] and parenteral[]" administration and, thus, could be formulated according to the recipes that existed with respect to prior art ophthalmic quinolone compositions. These prior art ophthalmic quinolone compositions included eye drops maintained at a pH of between 5 and 8. Likewise, the prior art reveals that disodium edetate is a conventional excipient with beneficial properties used in aqueous ophthalmic quinolone compositions. Multiple commercial and noncommercial quinolone compositions utilized disodium edetate in an amount of 0.01 w/v%, i.e., within the concentration range of 0.001 to 0.2 w/v% claimed by the '045 patent. Accordingly,

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[27]It is undisputed that the person of ordinary skill in the art would be skilled in the art of formulating aqueous pharmaceutical compositions as of August 21, 1998. This person would have a Ph.D. in pharmaceutics, pharmaceutical chemistry, or a closely related field, and at least two years of experience in formulating aqueous dosage forms. Alternatively, this person would have a lesser degree in an appropriate field and substantially more scientific training and practical experience in formulating aqueous pharmaceutical compositions. (*See* D.I. 107 at 319-20; D.I. 108 at 628-30)

the court concludes that defendants have presented a prima facie case of obviousness with respect to claims 1-3 and 9, i.e., that it would be obvious for one of ordinary skill to substitute the gatifloxacin of the '470 patent for any of the quinolones described by the '456 patent in the prior art quinolone compositions comprising disodium edetate in the amounts claimed by the '045 patent, with the reasonable expectation that it would result in an aqueous formulation.

b. Claim 6

Defendants rely upon the '456 patent, the '465 patent, the '470 patent and the Grass reference in arguing that the method of claim 6 is obvious. Plaintiffs correctly note that none of these references specifically disclose any impact by disodium edetate on the corneal permeability of any quinolone. In response, defendants argue that enhancing the corneal permeability of gatifloxacin by adding disodium edetate is not only obvious as a latent property of disodium edetate, but it would have been an expected feature of such compositions.

With respect to latency, defendants argue that the method of claim 6 merely combines two known constituents to result in a composition that exhibits the inherent property of increasing corneal permeability. According to defendants, this combination adds nothing new or patentable to an allegedly old and obvious method. *See Great Atl. & Pac. Tea Co. v. Supermarket Equip. Corp.*, 340 U.S. 147, 152 (U.S. 1950) (holding obvious a combination of old elements which perform the same function in combination and individually); *see also In re Baxter Travenol Labs*, 952 F.2d 388, 392 (Fed. Cir. 1991) ("Mere recognition of latent properties in the prior art does not render nonobvious

an otherwise known invention."). Latency, however, depends upon the presence of a known process. *See Bristol-Myers Squibb Co. v. Ben Venue Labs.*, 246 F.3d 1368, 1376 (Fed. Cir. 2001) (holding that "[n]ewly discovered results of **known processes** directed to the same purpose are not patentable because such results are inherent.") (emphasis added). Insofar as defendants have failed to identify a prior art disclosure concerning a process that explicitly discloses the addition of disodium edetate to gatifloxacin in solution, the latency argument must fail.

Alternatively, relying primarily on the Grass reference, defendants argue that one of ordinary skill would have expected disodium edetate to enhance the corneal permeability of gatifloxacin such that it would result in an increased concentration of gatifloxacin in the aqueous humor. With respect to the claimed concentration range of 0.001 to 0.2 w/v%, the record demonstrates that one skilled in the art would understand the Grass reference to suggest that EDTA concentrations lower than 0.5 w/v% would be effective in view of the increased corneal permeability of the 0.5 w/v% EDTA formulation to which calcium was added. Accordingly, one of ordinary skill would apply this teaching in conjunction with the pre-existing quinolone formulations, which incorporated between 0.05 and 0.1 w/v% EDTA, in arriving at a gatifloxacin formulation characterized by increased corneal permeability.

Contrary to this position, Dr. Stella testified that the teachings of the Grass reference have no bearing upon the obviousness of the invention of the '045 patent because the two studied compounds - glycerol and cromolyn - have no relationship with, and may well exhibit significant chemical and physical differences from, gatifloxacin. (D.I. 108 at 671-72) Dr. Stella's assertion is belied by the Grass

reference, which attributes the improved corneal permeability on the ability of EDTA to transport a **polar** compound across the epithelial layer of the cornea. While glycerol, cromolyn and gatifloxacin may exhibit chemical and physical differences, the parties do not dispute that each shares the only trait pertinent to the Grass reference - molecular polarity.

In anticipation of this interpretation, plaintiffs insist that, to the extent that the Grass reference discloses polar compounds as the sizable genus of substances suitable to trigger the corneal permeability enhancing properties of EDTA, the selection of gatifloxacin to achieve this result is not rendered obvious merely due to its status as a species of this genus. Plaintiffs cite to *In re Baird*, 16 F.3d at 382, for the proposition that "the fact that a claimed compound may be encompassed by a disclosed generic formula does not by itself render that compound obvious." Again, the available universe is not quite as broad as plaintiffs suggest. The Court in *In re Baird* made this statement in the context of a prior art disclosure of a genus that consisted of more than 100 million compounds. *Id.* By contrast, the genus disclosed by the Grass reference is not, as plaintiffs contend, any polar compound; rather, it is polar compounds that have a topical ophthalmic application.

Plaintiffs also emphasize defendants' failure to proffer a single reference in the 15 years between the publication of the Grass reference and the filing of the '045 patent that specifically discloses the use of EDTA to increase the corneal permeability of any drug. Irrespective of this period of alleged silence, one of ordinary skill is presumed to have knowledge of all pertinent prior art - be it obscure or unknown to

actual individuals.[28] *See, e.g., Custom Accessories, Inc. v. Jeffrey-Allan Industries, Inc.*, 807 F.2d 955, 962 (Fed. Cir. 1986); *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.*, 796 F.2d 443 (Fed. Cir. 1986). Certainly, the Grass reference meets the criteria of pertinency to warrant its inclusion among this hypothetical knowledge base.

Moreover, the validity of claim 6 does not hinge, as plaintiffs insist, upon the existence of a prior art teaching that EDTA affects the corneal permeability of gatifloxacin specifically, or even quinolones generally. Insofar as the parties agree that corneal permeability is a desirable property of a drug indicated for topical ophthalmic administration, creativity, at a minimum, would lead one of ordinary skill to place special value upon the teachings of the Grass reference. *See KSR*, 550 U.S. at 418-19. The likely compatibility of gatifloxacin and EDTA, made evident by the '456 and '470 patents, would only reinforce this value. At a minimum, within the finite range of excipients disclosed to be suitable in combination with quinolones, it would be obvious to try one such excipient characterized by the prior art as increasing the corneal permeability of polar compounds. *See id.* at 421. In view of the foregoing, the court concludes that defendants have demonstrated a prima facie case that the Grass reference, combined with the '470, '456 and '465 patents, would lead one of ordinary skill in the art to reasonably expect that, consistent with the court's construction of claim

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[28]Here, however, the Grass reference was known to Inada, and it was cited during the prosecution of the '045 patent. While Inada testified that he was aware of the Grass reference, he further explained that he believed that the disodium edetate concentration taught in this reference was higher than the invention of the '045 patent. (D.I. 107 at 462)

6, the step of adding disodium edetate (even at a concentration as low as 0.1 w/v%) to a solution of gatifloxacin eye drops would demonstrate an increased concentration of gatifloxacin in the aqueous humor.

c. Claim 7

Defendants argue that using disodium edetate to prevent the precipitation of gatifloxacin[29] is obvious as a latent property or, alternatively, that such a result would have been expected in view of the Riley reference, the '456 patent and the '470 patent. Having failed to identify a prior art process comprising the addition of disodium edetate to an aqueous solution of gatifloxacin and, for the reasons discussed, *supra*, defendants have not shown that this claim is obvious for disclosing a latent property of a known process. *See Bristol-Myers Squibb Co.*, 246 F.3d at 1376.

The court next considers whether the method of claim 7 would have been expected. As construed, the method of this claim requires disodium edetate in the amount of 0.001 to 0.2 w/v% to inhibit the precipitation of gatifloxacin in an aqueous solution. The court finds that, drawing upon the teachings of the Riley reference, one of ordinary skill in the art would predict that gatifloxacin, having a pK_a value similar to norfloxacin, ciprofloxacin, ofloxacin and lomefloxacin, would likewise display a similar and predictable solubility profile. Because gatifloxacin can be expected to behave similarly to these prior art quinolones in solution, one of ordinary skill would find apposite a further teaching of the Riley reference - that the addition of carboxylic acid will increase the solubility of a quinolone in the relevant pH range for topical ophthalmic

[29]The parties agree that it is undesirable for the active pharmaceutical ingredient to precipitate out of a topical ophthalmic solution. (D.I. 107 at 233-34, 310, 316-17)

administration.[30] The record demonstrates that the ability to increase the solubility of a quinolone using carboxylic acid bears a direct relationship to the ability to prevent or inhibit the quinolone from precipitating out of a solution.[31] (D.I. 107 at 349-58, 384)

In opposition to this understanding, Dr. Stella testified that the Riley reference merely demonstrates that quinolones and carboxylic acid behave unpredictably in solution. (D.I. 108 at 612) However, Dr. Stella conceded on cross examination that the Riley reference demonstrates a consistent increase in quinolone solubility at pH 5. (*Id.* at 668) Despite any unpredictability in quinolone solubility present in other pH ranges, this admitted positive effect on solubility falls squarely within the relevant pH range for topical ophthalmic applications. (D.I. 107 at 350-51; D.I. 108 at 668-69) The Riley reference attributes this increased solubility to one or both of two potential mechanisms: (1) complexation of the quinolone by the carboxylic acid; or (2) self association of the quinolones.[32] (D.I. 107 at 350-353, 453; *see also* JTX 15 at 34; D.I. 108 at 668)

In sum, one of ordinary skill in the art would understand from the Riley reference that adding carboxylic acids to aqueous formulations of quinolones would be reasonably expected to increase the solubility and, thereby, inhibit the precipitation, of

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[30]Ophthalmic compositions are suitable for topical administration over a pH range of 5-8. (*See* D.I. 107 at 335; *see also* '045 patent at claim 2)

[31]Plaintiffs argue that defendants have failed to demonstrate a link between the solubility studies reported in Riley and the prevention of precipitation specifically in a freeze-thaw study. (D.I. 112 at 32) This is a distinction without a difference, as neither the parties' proposed claim constructions, nor the court's actual construction, identifies a freeze-thaw limitation in the method of claim 7.

[32]Dr. Stella maintains that he proposed the self association theory and that his colleague authored the carboxylic acid mechanism. (D.I. 108 at 668)

the quinolones. As one of ordinary skill would predict gatifloxacin, based on its pK_a value, to display solubility characteristics similar to the quinolones studied in the Riley reference, it would be reasonable to assume that the addition of carboxylic acid to an aqueous solution of gatifloxacin would also inhibit the precipitation of gatifloxacin crystals from an aqueous solution. EDTA, an excipient known to be compatible with the quinolones studied in the Riley reference, contains four carboxylic acid groups. Finally, the '456 patent, as well as several prior art commercial quinolone products, teach the addition of EDTA in the claimed concentration range of 0.001 to 0.2 w/v%. Defendants have demonstrated, by clear and convincing evidence, a prima facie case that the Riley reference, in view of the '456 and '470 patents, renders the '045 patent obvious; i.e., one skilled in the art concerned with inhibiting the precipitation of gatifloxacin from an aqueous solution would reasonably expect to achieve this goal by adding a known compatible carboxylic acid excipient (such as EDTA) in the amounts taught by these prior art references to the aforementioned gatifloxacin solution.

d. Non-asserted claim 8

Defendants submit that the method of preventing the coloration of an aqueous gatifloxacin solution through the inclusion of 0.001 to 0.2 w/v% disodium edetate is rendered obvious by the Griffith reference. Plaintiffs primarily argue in response that there is no evidence that one of ordinary skill would have added disodium edetate to prevent the coloration of gatifloxacin because no prior art even indicated a discoloration issue with quinolones.

The evidence of record belies plaintiffs' position, as the prior art teaches that aqueous solutions of quinolones could become discolored by iron ions. (DTX 107 at

360; DTX 170 at col. 3:1-60) According to the Griffith reference, one of ordinary skill would understand that disodium edetate in concentrations from 0.005% to 0.4% would prevent discoloration caused by iron ions of many different pharmaceuticals. Even assuming, as plaintiffs contend, that the prior art did not describe the source of the coloration problem for quinolones, Dr. Myrdal testified that the first step that one skilled in the art would take when faced with such a problem would be to apply a chelating agent such as EDTA. Not only did plaintiffs' expert Dr. Stella fail to rebut this testimony, he testified that he could not defend the validity of claim 8.[33] (D.I. 108 at 631) Accordingly, defendants have demonstrated that the Griffith reference would lead one of ordinary skill to reasonably expect that adding disodium edetate to the gatifloxacin eye drops of the '470 patent would prevent any discoloration issues.

e. Secondary considerations

The parties have each proffered evidence of secondary considerations. In support of the prima face case of obviousness, defendants cite to Kyorin's independent prior formulation of aqueous ophthalmic gatifloxacin solutions containing disodium edetate. Plaintiffs argue that any showing of obviousness is mitigated through evidence of commercial success and unexpected results. The court addresses each in turn.

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[33]Q. And you told plaintiffs' counsel that you could not support the validity of claim 8, isn't that correct?

A. That's correct.

Q. Okay. And that is because you had had enough experience to know that you had seen EDTA prevent coloration in some products, and you felt you could not defend the validity of claim 8, isn't that correct?

A. That's correct.

i. Contemporaneous invention

The record demonstrates that, in 1995, a researcher at Kyorin independently[34] formulated several ophthalmic gatifloxacin solutions containing disodium edetate. (D.I. 100, ex. 1 at ¶ 25) One of these formulations bears a striking resemblance to example 1 of the '456 patent.[35] (DTX 19) Kyorin described these formulations as clear of precipitates after six months of storage at low temperature (5° C). Defendants argue that Kyorin's ophthalmic gatifloxacin solution containing disodium edetate is evidence that this formulation was within the ordinary skill in the art. *See Monarch Knitting Mach. Corp. v. Sulzer Morat GmbH*, 139 F.3d 877, 883 (Fed. Cir. 1998) ("[a]lthough this court has noted the relevance of contemporaneous independent invention to the level of ordinary knowledge or skill in the art, it has also acknowledged the view that this evidence is relevant as a secondary consideration . . . .") (internal citations omitted).

Monarch stands for the proposition that, while not dispositive of the obviousness inquiry, evidence of contemporaneous invention must be weighed "in light of all the circumstances, especially in light of evidence of long-felt need." *Id.* A subsequent case supports defendants' view that *Monarch* endorses the use of contemporaneous invention as a secondary consideration by itself and is not limited to rebutting evidence of long-felt but unsolved need. *See Boehringer Ingelheim Vetmedica, Inc. v.*

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[34]While Kyorin ultimately provided Senju with a gatifloxacin formulation, it did not contain EDTA. (JTX 36) None of the Kyorin researchers are listed as inventors of the '045 patent.

[35]Example 1 is also the formulation of BACCIDAL®, a commercially marketed norfloxacin solution. The only appreciable differences between these two formulations is the substitution of gatifloxacin for norfloxacin, and the absence of benzalkonium chloride in Kyorin's formulation. (DTX 19; '456 patent at col. 3:25-36)

Schering-Plough Corp., 68 F. Supp. 2d 508, 543 (D. N.J. 1999), *later opinion*, 166 F. Supp. 2d 19 (D.N.J. 2001), *aff'd*, 320 F.3d 1339 (Fed. Cir. 2003).

The court agrees that Kyorin's prior formulation is relevant to the question of obviousness, at least with respect to composition claims 1-3 and 9. At a minimum, the similarity between Kyorin's formulation and the formulation of the '456 patent lends credence to defendants' argument that one skilled in the art would have reason to combine the gatifloxacin disclosed by the '470 patent with disodium edetate pursuant to the formulation guidance provided by the '456 patent. This evidence reinforces a finding of obviousness with respect to claims 1-3 and 9.

With respect to the method claims, there is no evidence that Kyorin appreciated that this specific formulation had enhanced properties with respect to corneal permeability, precipitation or color prevention. Despite Kyorin's observation that its formulation resulted in a clear and colorless solution after nearly 6 months at low temperature storage, it is undisputed that Kyorin did not provide Senju with a formulation that contains EDTA. (JTX 36) An omission of this nature demonstrates that Kyorin did not recognize or appreciate the invention described by claims 6, 7 and 8. *See Boehringer*, 68 F. Supp. 2d at 544 ("the Court is not satisfied that [defendant] has presented sufficient evidence that [alleged contemporaneous inventors] cultured the PRRS virus or that they chose MA-104 cells for any particular reason other than that they were available at the time."). Accordingly, evidence of contemporaneous invention does not affect the obviousness inquiry with respect to claims 6, 7 and 8.

ii. Commercial success

Plaintiffs submit that the commercial success enjoyed by ZYMAR®, the undisputed commercial embodiment of the '045 patent, rebuts defendants' prima facie showing of obviousness. The Federal Circuit "deems evidence of (1) commercial success, and (2) some causal relation or 'nexus' between an invention and commercial success of a product embodying that invention, probative of whether an invention was nonobvious." *Merck & Co. v. Teva Pharms. USA, Inc.*, 395 F.3d 1364, 1376 (Fed. Cir. 2005). In this regard, plaintiffs have adduced evidence that ZYMAR® holds a 35% ophthalmology market share and has generated annual sales of approximately $100 million. Joe Schulz, Allergan's Senior Vice-President for U.S. Eyecare, testified for plaintiffs that Allergan marketed the product based on the formulation claimed by the '045 patent and, specifically, the formulation's ability to increase the corneal permeability of gatifloxacin. (D.I. 106 at 51-53)

Defendants argue that an inference of nonobviousness does not apply in the instance where an earlier patent precludes the market entry of generic products and the patentee attributes commercial success to a later patent on the product. *Id.* at 1377. The '470 patent, which claimed the compound gatifloxacin, did not expire until December 2009 and remains subject to pediatric exclusivity until June 15, 2010. Citing to *Merck*, defendants contend that, because others were legally barred from testing gatifloxacin products until the pediatric exclusivity associated with the '470 patent expires, the court may not find an inference of nonobviousness with respect to any alleged commercial success of ZYMAR®. *Id.* Consistent with the Federal Circuit's

holding that an inference of nonobviousness is weakened in such context,[36] the court attributes "minimal probative value" to the commercial success of ZYMAR®. *Id.*

iii. Unexpected results

Plaintiffs also argue that the increase in corneal permeability and inhibited precipitation were unexpected results of the combination of EDTA and gatifloxacin and, therefore, provide strong support for nonobviousness. Unexpected results exist when "the claimed invention exhibits some superior property or advantage that a person in the relevant art would have found surprising or unexpected." *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995). The Federal Circuit has explained the rationale for finding that unexpected results rebut a contention of obviousness as follows: "[T]hat which would have been surprising to a person of ordinary skill in a particular art would not have been obvious." *Id.* To the extent that the court determined, *supra*, that one of ordinary skill would expect the combination to exhibit each of these properties, this secondary consideration does not assist plaintiffs in rebutting defendants' prima facie case of obviousness.

f. Conclusion

Based on the foregoing, the court finds that, taken as a whole, the secondary considerations favor neither party and do not change the obviousness determination discussed above. Therefore, defendants have demonstrated, by clear and convincing evidence, that claims 1-3 and 6-9 are invalidated as rendered obvious by the asserted

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[36]As opposed to vitiated, as defendants contend. *See id.* (finding that where an earlier patent blocks entry of generic products into the market, a weak inference of commercial success may be attributed to a later patent on the product.).

prior art.

C. Enablement

1. Legal standard

The statutory basis for the enablement requirement is found in 35 U.S.C. § 112, paragraph 1, which 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). 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). The enablement requirement is a question of law based on underlying factual inquiries. *Wands*, 858 F.2d at 737.

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).

A discrete, but related, inquiry considers the presence of inoperative embodiments and informs the enablement inquiry. *National Recovery Techs. Inc. v. Magnetic Separation Sys. Inc.*, 166 F.3d 1190, 1196 (Fed. Cir. 1999). Pursuant to this inquiry, a claim is invalid for lack of enablement "if it reads on a significant number of inoperative embodiments." *Crown Operations Int'l, LTD v. Solutia Inc.*, 289 F.3d 1367, 1381 (Fed. Cir. 2002) (internal citations omitted).

2. Discussion

Defendants contend that method claims 6 and 7 are not enabled insofar as they fail to limit the pH or concentration levels of either gatifloxacin or disodium edetate, and that many permutations of these variables within this allegedly broad scope do not result in increased permeability or prevention of precipitation. The court addresses defendants' arguments *vis a vis* each claim.

a. Claim 6

According to defendants, the claimed range of 0.001 to 0.2 w/v% disodium edetate to a gatifloxacin solution does not per se result in increased corneal permeability. In support of this argument, defendants primarily rely upon the testimony of Dr. Myrdal, who contends that, based on the Grass reference, the low end of the claimed concentration range of EDTA will not work to increase corneal permeability. (D.I. 107 at 381) The slide that Dr. Myrdal used to illustrate this point consists of a line bar depicting a range of EDTA concentrations from below 0.001 to above 0.5 w/v%.

(DTX 194 at 140) The line bar also depicts Dr. Myrdal's conclusion that EDTA, at a concentration somewhere above 0.001 w/v%, would be expected to increase corneal permeability. (*Id.*) However, neither the line bar nor Dr. Myrdal identifies a discrete concentration at which this functional transition occurs. Defendants also allege that the failure to enable claim 6 is implicit in a report by Yasueda showing that, "at the same one-hour time point used in the patent as the marking point for corneal permeability, formulation C (gatifloxacin with disodium edetate) showed no increase in permeability over formulation B (gatifloxacin alone)." (D.I. 110 at 40; JTX 24 at 10-12) The parties' experts agree that there is no statistical difference between the two formulations at the one-hour time point in this study. (D.I. 107 at 365-67)

Dr. Myrdal's ambiguous conclusion that a portion of the claimed range would "likely" not have an effect on corneal permeability does not establish clear and convincing evidence of invalidity. Even assuming defendants have identified a single one-hour data point that may correspond to an inoperable embodiment, this evidence, too, suffers from a similar deficiency.[37] This is because, "[e]ven if some of the claimed combinations [are] inoperative, the claims are not necessarily invalid." *Atlas Powder Co. v. E. I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1576 (Fed. Cir. 1984). To the extent that defendants have alleged a lack of enablement based on inoperable embodiments, defendants must show that claim 6 "reads on significant numbers of inoperative embodiments." *Crown*, 289 F.3d at 1380. The court concludes that defendants have made no such showing and, therefore, have failed to demonstrate, by

[37]The court addresses defendants' characterization of the results of this test *infra*.

clear and convincing evidence, that one of ordinary skill cannot practice the full scope of the method of claim 6 without undue experimentation.

b. Claim 7

Defendants likewise allege that claim 7 fails to satisfy the enablement requirement because it reads upon multiple inoperable embodiments. In this regard, defendants contend that, contrary to the method of claim 7: (1) both sodium chloride and disodium edetate are required to prevent precipitation; and (2) certain compositions would not precipitate regardless of the inclusion of disodium edetate.

With respect to the first alleged ground, defendants note that testing by Yasueda demonstrates that combining only EDTA and gatifloxacin into an aqueous composition does not prevent precipitation. (JTX 23 at 7) Instead, defendants contend that sodium chloride is required as well. (*See id.* at 7-8) In response, plaintiffs submit the results of two formulations in this study, E-1 and E-3. Neither of these formulations contained sodium chloride. (*Id.* at 3) Yasueda determined that formulation E-3, which contained 0.05 g disodium edetate, precipitated after 2 freeze-thaw cycles, and that formulation E-1, which contained 0.1 g disodium edetate, precipitated after 3 freeze-thaw cycles. (*Id.* at 8) Consequently, despite a showing that sodium chloride further assists in preventing the precipitation of aqueous gatifloxacin compositions containing EDTA, the evidence of record demonstrates that increasing the amount of EDTA hindered the precipitation of formulations without sodium chloride. Because claim 7, as construed, only requires disodium edetate to "hinder the progress of" the precipitation of gatifloxacin, defendants have failed to demonstrate a lack of enablement in this regard.

Defendants next argue that, in the study performed by Yasueda, precipitation did not occur in several of the formulations that did not contain EDTA. The court agrees that EDTA cannot act to prevent what would not occur to begin with. However, there is no failure to satisfy the enablement requirement for claiming substantial inoperable embodiments if one of ordinary skill possesses the "necessary information to limit the claims to operative embodiments . . . ." *Crown*, 289 F.3d at 1380 (citing *In re Cook*, 439 F.2d 730, 735 (CCPA 1971)). Here, the record demonstrates that one of ordinary skill would recognize that certain aqueous gatifloxacin compositions would not exhibit precipitation. (DTX 194 at 143) The mere fact that a solution does not precipitate to begin with would logically obviate the need to consider a remedy concerning the prevention of precipitation. These instances must be excluded from the inoperative embodiment inquiry. In accordance with the findings above, the court concludes that defendants have failed to demonstrate, by clear and convincing evidence, that claim 7 is invalid for lack of enablement.

D. Enforceability

1. Legal standard

Applicants for patents and their legal representatives have a duty of candor, good faith, and honesty in their dealings with the United State Patent and Trademark Office ("PTO"). *Molins PLC v. Textron, Inc.*, 48 F.3d 1172, 1178 (Fed. Cir. 1995); 37 C.F.R. § 1.56(a) (2003). The duty of candor, good faith, and honesty includes the duty to submit truthful information and the duty to disclose to the PTO information known to the patent applicants or their attorneys which is material to the examination of the

patent application. *Elk Corp. of Dallas v. GAF Bldg. Materials Corp.*, 168 F.3d 28, 30 (Fed. Cir. 1999). A breach of this duty constitutes inequitable conduct. *Mollins*, 48 F.3d at 1178. If it is established that a patent applicant engaged in inequitable conduct, the patent application is rendered unenforceable. *Kingsdown Med. Consultants v. Hollister Inc.*, 863 F.2d 867, 877 (Fed. Cir. 1988).

In order to establish unenforceability based on inequitable conduct, a defendant must establish, by clear and convincing evidence, that: (1) the omitted or false information was material to patentability of the invention; or (2) the applicant had knowledge of the existence and materiality of the information; and (3) the applicant intended to deceive the PTO. *Mollins*, 48 F.3d at 1178. A determination of inequitable conduct, therefore, entails a two step analysis. First, the court must determine whether the withheld information meets a threshold level of materiality. A reference is considered material if there is a substantial likelihood that a reasonable examiner would consider it important in deciding whether to allow the application to issue as a patent. *Allied Colloids, Inc. v. American Cyanamid Co.*, 64 F.3d 1570, 1578 (Fed. Cir. 1995) (citations omitted). A reference, however, does not have to render the claimed invention unpatentable or invalid to be material. *See Merck v. Danbury Pharmacal*, 873 F.2d 1418 (Fed. Cir. 1989).

After determining that the applicant withheld material information, the court must then decide whether the applicant acted with the requisite level of intent to mislead the PTO. *See Exergen Corp. v. Wal-Mart Stores, Inc.*, 575 F.3d 1312, 1327 (Fed. Cir. 2009); *Baxter Int'l, Inc. V. McGaw Inc.*, 149 F.3d 1321, 1327 (Fed. Cir. 1998). "Intent to

deceive cannot be inferred solely from the fact that information was not disclosed; there must be a factual basis for finding a deceptive intent." *Herbert v. Lisle Corp.*, 99 F.3d 1109, 1116 (Fed. Cir. 1996). That is, "the involved conduct, viewed in light of all the evidence, including evidence indicative of good faith, must indicate sufficient culpability to require a finding of intent to deceive." *Kingsdown*, 863 F.2d at 876 (Fed. Cir. 1988). Evidence of specific intent must "be clear and convincing, and inferences drawn from lesser evidence cannot satisfy the deceptive intent requirement." *Star Sci., Inc. v. R.J. Reynolds Tobacco Co.*, 537 F.3d 1357, 1366 (Fed. Cir. 2008). A "smoking gun" is not required in order to establish an intent to deceive. *See Merck*, 873 F.2d at 1422.

Once materiality and intent to deceive have been established, the trial court must weigh them to determine whether the balance tips in favor of a conclusion of inequitable conduct. *N.V. Akzo v. E.I. DuPont de Nemours*, 810 F.2d 1148, 1153 (Fed. Cir. 1988). The showing of intent can be proportionally less when balanced against high materiality. *Id.* In contrast, the showing of intent must be proportionally greater when balanced against low materiality. *Id.*

2. Discussion

Defendants contend that Yasueda and Inada made material misrepresentations and withheld material data bearing upon the claimed corneal permeability and precipitation properties during the prosecution of the '045 patent. According to defendants, several instances of withheld data belie the applicants' conclusions that the invention of the '045 patent demonstrated increased corneal permeability and prevented precipitation.

With respect to the claims of increased corneal permeability, defendants propound that the results of the studies contained in the research reports contradict the conclusions asserted in the application for the '045 patent, namely, that adding disodium edetate increased the corneal permeability of an aqueous gatifloxacin composition by a multiple of 1.2 to 1.5.[38] First, defendants assert that the data presented by table 2 of the '045 patent is based on a "vanishingly small" sample size of testing. Defendants theorize that the inventors withheld the sample size so as to prevent the examiner from discovering the statistical insignificance of the presented results. Specifically, defendants contend that the sample of three eyes for formulation B and five eyes for formulation C created "exceeding unreliable" results.

As a preliminary matter, defendants have not identified any requirement of the patent laws regarding statistical significance. Of course, the failure to disclose a small sample size could still fall within the ambit of materiality if, for example, the applicants told the examiner that the disclosed results met the FDA's requirement for statistical significance, or statistical significance was otherwise heralded in the specification of the '045 patent. Defendants have adduced no such evidence. In fact, contrary to defendants' theory that plaintiffs only provided the PTO with results that favored the claim of increased corneal permeability, the evidence of record demonstrates that the applicants included in the data for table 2 of the '045 patent an inconsistent and potentially unreliable data point which tended to militate against a showing of increased

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[38]Defendants state that the applicants asserted a 50% increase, however, the '045 patent discloses that the expected range of increase is between "about 1.2 times and 1.5 times." ('045 patent at col. 4:1-5)

corneal permeability. Dr. Jennifer Elder ("Dr. Elder"), defendants' statistical analysis expert, testified that without this "outlier" data point, formulation C has a statistically significantly higher corneal permeability than formulation A and B. (D.I. 108 at 508-511) The court concludes that the applicants' failure to disclose the sample size associated with table 2 did not result in a material omission.

Next, defendants contend that the applicants knowingly failed to disclose data tending to demonstrate that disodium edetate has no meaningful effect upon corneal permeability. In support of this theory, defendants note that, at the one-hour time point used in the patent as the marking point for increased corneal permeability, a second undisclosed study of formulations B and C revealed no appreciable difference in corneal permeability. (JTX 24 at 12) Defendants further allege that Yasueda recognized the significance of these results when he reported that the aqueous humor migration was "virtually the same." (*Id.*)

Viewing Yasueda's remarks within the context of the entire passage from which they are taken,[39] the court finds that they concern the relative aqueous humor migrations of gatifloxacin and levofloxacin, and do not compare formulation B with formulation C. Moreover, the unrebutted testimony of Dr. Matthew Mayo ("Dr. Mayo") establishes that the experiment that generated the results of table 9 was not designed to look at the amount of gatifloxacin in the aqueous humor at a specific time. (D.I. 108

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[39]The full sentence reads: "**The [gatifloxacin] and levofloxacin aqueous humor migration** after instillation with 0.5% [gatifloxacin] ophthalmic solution, 0.5% [gatifloxacin] solution including 0.05% [disodium edetate], and 0.5% levofloxacin solution **were virtually the same in aqueous humor concentration and AUC_{0-4} at the various times**." (*Id.*) (emphasis added)

at 554) Instead, the appropriate baseline comparison is the total concentration of gatifloxacin measured in the aqueous humor over the entire span of the experiment, which is illustrated by the AUC. Table 10 reflects this data and confirms the conclusion set forth by the '045 patent, i.e., that formulation C (which contained disodium edetate) demonstrated a corneal permeability approximately 1.46 times that of formulation B (which did not contain disodium edetate). (JTX 24 at 13) The applicants' failure to disclose the results of table 9 did not result in a material omission.

With respect to the applicants' alleged material omissions of precipitation data, defendants argue that Yasueda failed to inform the examiner that both disodium edetate and sodium chloride are required to prevent the precipitation of gatifloxacin. Defendants allege that this requirement is made evident by comparing the absence of precipitation in formulations B and C (both of which contained sodium chloride) with the eventual precipitation of formulations E-1 and E-3 (neither of which contained this component). Yasueda's awareness regarding the necessity of sodium chloride is allegedly captured in the research reports in which he notes that, "[i]n the case of solutions containing both [disodium edetate] and sodium chloride, a crystal precipitate preventative action was observed for 0.5% [gatifloxacin] ophthalmic solution (pH 6.0)." (JTX 23 at 7-8) According to defendants, this contradicts the applicants' claims that disodium edetate alone prevents precipitation.

Defendants' arguments are unavailing under the court's construction of "preventing precipitation," which is properly defined as hindering the progress of precipitation. *See Agfa Corp. v. Creo Prods.*, 451 F.3d 1366, 1377 (Fed. Cir. 2006) (acknowledging the interrelationship of materiality and claim construction). As

mentioned, *supra*, formulations E-1 and E-3 were identical aside from a greater concentration of EDTA in formulation E-1. The test results for these formulations established that it took longer, i.e., more freeze-thaw cycles were required, for formulation E-1 to precipitate. Such a result is entirely consistent with the meaning of "preventing precipitation." Moreover, Yasueda's statement is inapposite to the materiality inquiry to the extent that he made no comment that a precipitation effect was **only** observed in solutions containing sodium chloride. Accordingly, because the data from formulations E-1 and E-3 establishes that EDTA acts to prevent precipitation within the meaning of the '045 patent, this is cumulative of the other data submitted by the applicants in support of experiment 2. *See* 37 C.F.R. § 1.56(b).

An additional material omission allegedly arises from the applicants' failure to submit the results of tests showing that multiple gatifloxacin solutions made without disodium edetate did not precipitate. The evidence adduced at trial, however, establishes that one of ordinary skill would understand that the solubility of gatifloxacin, established above to be directly related to precipitation potential, was highly dependent upon pH. (D.I. 107 at 434-36) The '045 patent discloses this pH dependency. Accordingly, this undisclosed testing is consistent with, and cumulative of, other disclosures contained in the '045 patent and cannot form a basis for a material omission.

In view of the foregoing, the court concludes that the applicants did not make material misstatements or withhold material information during the prosecution of the '045 patent. Having concluded as such, the court does not reach the issue of intent to deceive. Defendants have failed to demonstrate, by clear and convincing evidence,

that the '045 patent is unenforceable on the basis that it was procured by inequitable conduct.

IV. CONCLUSION

For the reasons discussed above, the court concludes that plaintiffs have proven, by a preponderance of the evidence, that defendants infringe claims 1-3, 6, 7 and 9 of the '045 patent. Defendants have demonstrated, by clear and convincing evidence, that claims 1-3 and 6-9 are invalid as obvious. Defendants have failed to prove, by clear and convincing evidence, that claims 6 and 7 are invalid for lack of enablement. Likewise, defendants have failed to prove, by clear and convincing evidence, that the '045 patent is unenforceable for inequitable conduct. Having found no basis to conclude that this case is exceptional, the parties shall bear their own costs. An appropriate order shall issue.

IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

SENJU PHARMACEUTICAL CO. LTD., KYORIN PHARMACEUTICAL CO. LTD. and ALLERGAN, INC.	)	
Plaintiffs,	)	
v.	)	Civ. No. 07-779-SLR
APOTEX INC. and APOTEX CORP.	)	
Defendants.	)	

ORDER

At Wilmington this 14th day of June, 2010, consistent with the memorandum opinion issued this same date;

IT IS ORDERED that:

1. Plaintiffs have demonstrated, by a preponderance of the evidence, that defendants' ANDA product infringes claims 1-3, 6, 7 and 9 of U.S. Patent No. 6,333,045.

2. Defendants have demonstrated, by clear and convincing evidence, that claims 1-3 and 6-9 of U.S. Patent No. 6,333,045 are rendered obvious by the prior art.

3. Defendants have failed to demonstrate, by clear and convincing evidence, that claims 6 and 7 of U.S. Patent No. 6,333,045 are invalid for lack of enablement.

4. Defendants have failed to demonstrate, by clear and convincing evidence, that U.S. Patent No. 6,333,045 is unenforceable because it was procured through inequitable conduct.

5. The Clerk of Court is directed to enter judgment in favor of defendants and

against plaintiffs.

United States District Judge