

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.)
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Defendants.)
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OPINION

Dated: December 20, 2011
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 ¶ 7) The ‘045 patent is directed to aqueous liquid pharmaceutical compositions comprising gatifloxacin and disodium edetate, as well as various methods utilizing these compositions. (‘045 patent at col. 1:7-57) 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, sold under the trade name ZYMAR®. (D.I. 100, ex. 1 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, 21)

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.

¹No. 02-1493. (D.I. 100, ex. 1 at ¶ 9)

²The ‘470 patent was issued to Kyorin in 1990 and expired on December 15, 2009. (D.I. 122 at 1) Pediatric exclusivity associated with the ‘470 patent ended 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.*)

³No. 79-084. (D.I. 100, ex. 1 at ¶ 13)

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 letter informing plaintiffs that the ANDA contained a Paragraph IV certification⁴ for the ‘045 patent. (*Id.* at ¶ 17) Therein, defendants asserted that the ANDA product would not infringe claims 4, 5, 10 and 11 of the ‘045 patent and that all the claims of the ‘045 patent were invalid. (*Id.* at ¶ 18)

Plaintiffs brought an infringement action on November 29, 2007 pursuant to 35 U.S.C. § 271(e)(2)(A), alleging that the ANDA product would infringe claims 1-3, 6, 7 and 9 of the ‘045 patent. (D.I. 1 at ¶¶ 32, 33) Defendants responded with affirmative defenses and counterclaims seeking declaratory judgment of noninfringement, invalidity and unenforceability of the ‘045 patent. (D.I. 63) While defendants maintained that claims 6 and 7 would not be infringed, the parties stipulated that, if valid, the ANDA product would infringe claims 1-3 and 9 of the ‘045 patent. (D.I. 100, ex. 2 at 1) The court held a claim construction hearing on December 4, 2009. A bench trial was conducted on January 12-14, 2010.

Thereafter, the court made the following findings of fact and conclusions of law pursuant to Fed. R. Civ. P. 52(a): (1) defendants’ ANDA product infringed claims 1-3, 6, 7, and 9 of the ‘045 patent; (2) defendants demonstrated that claims 1-3 and 6-9 of the ‘045 patent are rendered obvious by prior art; (3) defendants failed to demonstrate that claims 6 and 7 of the ‘045 patent are invalid for lack of enablement and; (4) defendants failed to demonstrate inequitable conduct. (D.I. 123)

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

Plaintiffs motioned for a new trial or, alternatively, to amend judgment and findings regarding claim 7. (D.I. 126) Plaintiffs asserted that defendants relied on evidence which was outside of defendants' expert report on obviousness and that this evidence was not properly disclosed or vetted during discovery. (*Id.*) Specifically, plaintiffs argued that defendants cited, and the court relied upon, disclosures from a 1989 article by Riley et al. ("the Riley reference"), to show a link between solubility and precipitation. (*Id.* at 5) Plaintiffs contend that information from this article, used in the trial, was outside of Dr. Myrdal's expert report.⁵ (*Id.*) On November 3, 2010, the record was reopened regarding claim 7. (D.I. 129) An evidentiary hearing was held on April 27 and May 4, 2011 to allow for further evidence on the relationship between precipitation and solubility, as detailed *infra*. (D.I. 139)

II. SUPPLEMENTAL FINDINGS OF FACT AND CONCLUSIONS OF LAW

A. The Parties

1. 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. (D.I. 122 at 3) Kyorin is a Japanese corporation with its principal place of business in Tokyo, Japan. (D.I. 100, ex. 1 at ¶ 2) Kyorin engages in the development of pharmaceuticals directed to infectious, immunological, allergic and metabolic diseases. (D.I. 122 at 3) Allergan is a corporation formed under the laws of the State of Delaware, having its principal place of business in Irvine, California. (D.I. 100, ex. 1 at ¶ 3) Allergan develops and sells

⁵Dr. Paul Myrdal ("Dr. Myrdal").

pharmaceuticals, biologics and medical devices. (D.I. 122 at 3)

2. Apotex Corp. is a corporation formed under the laws of the State of Delaware, having its principal place of business in Weston, Florida. (D.I. 100, ex. 1 at ¶ 4) Apotex Corp. offers for sale and sells numerous generic drugs manufactured and supplied by Apotex Inc., a corporation formed under the laws of Canada, having its principal place of business in Ontario, Canada. (D.I. 13 at ¶ 6; D.I. 100, ex. 1 at ¶ 5) Apotex Inc. primarily develops, manufactures and commercializes generic pharmaceutical products. (D.I. 13 at ¶ 8)

B. Technology at Issue

1. Quinolones

3. Fluoroquinolones, otherwise known as quinolone carboxylic acids or simply “quinolones,” are a class of broad spectrum antibacterial compounds that share a common core chemical structure. (D.I. 107 at 326:19-20; ‘470 patent at col. 1:7-13) A carboxylic acid, along with a nitrogen-containing carbon ring and a double-bonded oxygen, are fundamental and common aspects of all quinolone antibiotics. (‘470 patent at col. 2:12-25)

4. The ‘470 patent was before the examiner during the prosecution of the ‘045 patent and claims gatifloxacin⁶ and its acid derivatives. (*Id.* at col. 1:1-8) The properties of gatifloxacin, a fourth generation quinolone, are revealed following a discussion of previously discovered quinolones, to wit, norfloxacin, ofloxacin and

⁶The International Union of Pure and Applied Chemistry (“IUPAC”), or systematic, name for gatifloxacin is 1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7(3-methyl-1-piperaziny)-4-oxo-3-quinoline carboxylic acid.

ciprofloxacin. (*Id.* at col. 1:32-61) The '470 patent explains that each of the disclosed quinolones have "similar substituents." (*Id.* at col. 1:41-43)

2. The '045 patent

5. On December 25, 2001, the '045 patent, entitled "Aqueous Liquid Pharmaceutical Composition Comprised of Gatifloxacin," was issued listing Shinichi Yasueda and Katsuhiko Inada ("Mr. Inada") as inventors. (D.I. 100, ex. 1 at ¶ 6) The '045 patent discloses gatifloxacin as a new quinolone with antimicrobial activity. ('045 patent at col. 1:19-20) The object of the '045 patent was to invent an aqueous liquid pharmaceutical composition comprising gatifloxacin for topical administration, applicable in the ophthalmological or otorhinological field. (*Id.* at col. 1:40-50) The '045 patent's summary discloses improved solubility of gatifloxacin at physiological pH due to the coexistence of disodium edetate. (*Id.* at col. 2:13-14)

6. At issue in this case is claim 7 of the '045 patent, which describes a method for preventing the precipitation of gatifloxacin crystals and comprises the incorporation of disodium edetate into an aqueous liquid preparation containing gatifloxacin or its salt. (*Id.* at col. 8:42-45)

3. The prior art

a. Primary references

7. At trial, Dr. Myrdal testified that, in the context of quinolone solution chemistry, variations in functional groups among the quinolones named by the '470 patent are "really not from a physical/chemical standpoint huge differences." (D.I. 107 at 327:1-2) Generally, while different functional groups may result in some differences in solubility,

one of skill in the art can expect a relatively predictable pH-dependent solubility profile for these quinolones. (*Id.* at 351:12-15)

8. Dr. Myrdal relied on the Riley reference, which proposed several simulated solubility profiles for quinolones.⁷ (D.I. 108 at 665:13-15) The Riley reference demonstrates that quinolones with similar pK_a ⁸ values exhibit a U-shaped solubility curve with an inflection point around each of the pK_a values. (JTX-015 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 of 5 resulted in the increased solubility of the quinolone. (*Id.*)

9. Disodium edetate (commonly known as “EDTA”) has four carboxylic acid groups. (D.I. 107 at 354:9-10; D.I. 108 at 669:15-16) EDTA is the disodium salt of ethylenediamine tetraacetic acid.⁹ (D.I. 100, ex. 1 at ¶ 40) EDTA, a multi-purpose

⁷Plaintiffs’ expert, Dr. Valentino Stella (“Dr. Stella”), co-authored this paper. (D.I. 108 at 664:22-23)

⁸In 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. (D.I. 122 at 8)

⁹Because 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.

excipient,¹⁰ is widely known as a chelating agent.¹¹ (D.I. 107 at 332:10; DTX-166 at 109)

10. U.S. Patent No. 4,551,456 (“the ‘456 patent”), teaches that quinolones¹² are “compatible with ocular tissue” and useful in treating bacterial ocular infections through topical administration. (‘456 patent at col. 1:13-31) The ‘456 patent discloses EDTA in a list of 8 excipients described as “conventional ingredients” in ophthalmic compositions. (*Id.* at col. 2:5-9) One of two exemplary ophthalmic compositions disclosed by the ‘456 patent is an aqueous solution of 0.3 w/v% norfloxacin and 0.01 w/v% disodium edetate. (*Id.* at col. 3:25-36)

11. U.S. Patent No. 4,780,465 (“the ‘465 patent”) discloses aqueous compositions for the quinolone lomefloxacin and characterizes disodium edetate as a conventional excipient. (‘465 patent at col. 2:31-46) The ‘465 patent addressed the low solubility exhibited by lomefloxacin solutions containing sodium chloride, another common eye drop excipient. (*Id.* at col. 3:7-20) The inventors of the ‘465 patent solved these solubility issues with a polyalcohol or boric acid instead of sodium chloride in the composition. (*Id.* at col. 2:1-8) Nevertheless, two exemplary ophthalmic compositions

¹⁰The 1986 Handbook of Pharmaceutical Excipients discloses that EDTA, in addition to its chelating function, may act as an antibacterial synergist/preservative enhancer. (DTX-166 at 110)

¹¹A chelating agent can form stable complexes with certain undesirable ions (generally metals), thereby removing them from solution. (D.I. 107 at 332:10-17) This chelating effect is achieved in EDTA through its four carboxylic acid groups which serve to wrap around these ions, forming complexes with metal ions and remove the metal ions from solution. (DTX-166 at 109)

¹²Quinolones discussed include norfloxacin, ofloxacin, and perfloxacin. (JTX-013)

described in the '465 patent, similar to the ophthalmic composition disclosed by the '456 patent ('456 patent at col. 3:25-36), contain 0.3 w/v% lomefloxacin and 0.01 w/v% disodium edetate. ('465 patent at col. 4:1-23)

C. Procedural Posture

1. The June 14, 2010 memorandum opinion

12. The court concluded in its opinion 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.” (D.I. 122 at 30) The Riley reference would teach one of ordinary skill that the “addition of carboxylic acid will increase the solubility of a quinolone in the relevant pH range for topical ophthalmic administration.”¹³ (*Id.*) The record demonstrated 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.” (*Id.* at 31) The court then ruled that defendants demonstrated,

by clear and convincing evidence, a prima facie case that the Riley reference, in view of the '456 patent and the '470 patent, 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.

(*Id.* at 32)

¹³Ophthalmic compositions are suitable for topical administration over a pH range of 5-8. (D.I. 107 at 335:1-2)

2. Plaintiffs' June 28, 2010 motion

13. Plaintiffs filed a motion pursuant to Fed. R. Civ. P. 59(b) for a new trial regarding the validity of claim 7. (D.I. 126 at 1) In the alternative, plaintiffs moved: (1) under Fed. R. Civ. P. Rule 52(b), for amended or additional findings; (2) under Fed. R. Civ. P. Rule 59(e), to alter or amend a judgment; (3) under Fed. R. Civ. P. Rule 60(b), for relief from a final judgment, order, or proceeding and; (4) under D. Del. L.R. 7.1.5, for this court to find that defendants failed to show that claim 7 was invalid by clear and convincing evidence. (*Id.*) Plaintiffs allege that defendants' reliance on evidence not vetted during discovery resulted in manifest injustice. (*Id.* at 6) Specifically, plaintiffs allege that they were unfairly surprised by evidence of tutorial¹⁴ and arbitrary U curves¹⁵ introduced by defendants that were not part of Dr. Myrdal's pre-trial expert report. (*Id.* at 3-4) The tutorial and arbitrary U curve slides were purportedly prepared by Dr.

¹⁴Plaintiffs refer to the powerpoint slides admitted at trial: (1) slide 1 is an overview of Dr. Myrdal's presentation; (2) slide 2 explains formulation considerations; (3) slide 3 explains solubility testing; (4) slide 4 is a chart explaining solubility as a function of pH; (5) slide 5 is a schematic demonstrating the pH solubilization of an acidic group; (6) slide 6 is a schematic demonstrating pH solubilization of a basic group; (7) slide 7 depicts pH solubilization of a zwitterion (1 Acidic and 1 Basic Group); (8) slide 8 lists conventional excipients/dosage forms; (9) slide 9 explains the stability of the formulation and; (10) slide 10 lists knowledge in the relevant field. (DTX-194 at 1-10)

¹⁵Plaintiffs refer to powerpoint slides admitted at trial: (1) slide 5 is a schematic demonstrating the pH solubilization of an acidic group; (2) slide 6 is a schematic demonstrating pH solubilization of a basic group; (3) slide 7 depicts pH solubilization of a zwitterion (1 Acidic and 1 Basic Group); (4) slide 105 depicts risks of precipitation without disodium edetate; (5) slide 106 depicts the same as slide 105, with a shaded area at room temperature; (6) slide 107 is the same as slide 106; (7) slide 108 depicts disodium edetate would be reasonably expected to raise solubility; (8) slide 143 depicts disodium edetate would be reasonably expected to raise solubility only over a narrow range and; (9) slide 144 shows the same as slide 143. (DTX-194 at 5-7, 105-108, 143 and 144)

Myrdal to “demonstrate the interplay between solubility and precipitation.” (*Id.* at 1; D.I. 129 at ¶ 1) That is, Dr. Myrdal incorporated findings from the Riley reference into these slides to “demonstrate the concept of precipitation that was occurring” in the Riley studies. (D.I. 107 at 354:18-23) Plaintiffs allege that defendants never provided the slides yet relied upon them to show a link between solubility and precipitation in the assertion of the obviousness of claim 7. (D.I. 126 at 5) Plaintiffs argued that the court relied on the slides in finding for defendants. (*Id.*) According to plaintiffs, defendants’ evidence showed that the “use of EDTA to prevent precipitation from a preexisting solution was unknown, surprising, and unexpected” and, therefore, defendants’ evidence was not clear and convincing. (*Id.* at 6)

3. The November 3, 2010 order to open the record

14. Although plaintiffs’ motion was dismissed without prejudice to renew, the court opened the record of this litigation pursuant to Fed. R. Civ. P. 59(a)(2). (D.I. 129)

The court determined that plaintiffs’ motion

calls into question what defendants (and this court) have operated upon as a basic principle of science, to wit, that solubility and precipitation bear to some extent an inverse relationship to each other. Upon review of the record, the development of this concept seems to have generated very little attention during discovery.

(*Id.* at 5) The court noted that

plaintiffs point to a single statement bearing upon this relationship in the invalidity portion of Dr. Myrdal’s expert report, in which he cites to a treatise by Martin et al. (“the Martin reference”) for the basis of his opinion that [a] person of ordinary skill in the art at the time the ‘045 patent was applied for would have known that one method for preventing precipitation of the active ingredient in a solution, such as those disclosed in the ‘456 and ‘465 patents, under set conditions, is to modify the formulation to raise the active ingredient’s solubility.

(*Id.*; D.I. 126, ex. 1 at ¶ 88) The court agreed with plaintiffs that the Martin reference discussed solubility yet did not disclose a link to precipitation. (D.I. 129 at 5) The court further noted that

in his opinion as to the enablement of the '045 patent, Dr. Myrdal notes that whether gatifloxacin precipitates is "predominantly controlled" by its solubility at a given pH and temperature. (D.I. 127, ex. 2 at ¶ 65) Similarly, in Dr. Myrdal's rebuttal noninfringement report, he consistently submits that "a person of ordinary skill in the art would understand that temperature and pH affect the solubility of a drug and, thus, whether it precipitates." (*Id.*, ex. 3 at ¶ 63) These opinions did not elicit a specific line of questioning during plaintiffs' deposition of Dr. Myrdal as to the interplay between these two properties. It is clear from this record that plaintiffs did not attribute as much significance as did defendants to the relationship between solubility and precipitation and, consequently, this issue was not properly vetted during discovery.

(D.I. 129 at 6) The court, therefore, reopened the record to allow for additional evidence regarding the relationship between solubility and precipitation. (*Id.*)

D. Evidence Presented at the April 27 and May 4, 2011 Hearings

15. In response to the court's order, plaintiffs offered expert testimony and conducted freeze-thaw experiments with norfloxacin and EDTA (hereinafter, "the norfloxacin tests"),¹⁶ to determine whether EDTA hinders the precipitation of norfloxacin.

(D.I. 144 at 10) Norfloxacin is a compound within the quinolone family and structurally similar to gatifloxacin, as discussed in the '045 patent. (*Id.* at 25) Plaintiffs selected norfloxacin because defendants argued, during trial, that "based on the Riley reference and the '456 patent, structurally related quinolones, such as norfloxacin, would be expected to have similar properties." (*Id.*) Plaintiffs conducted the norfloxacin tests

¹⁶The norfloxacin tests, discussed *infra*, were freeze-thaw tests of norfloxacin. This type of test involves repeat freezing and thawing cycles of norfloxacin solutions to determine the presence of precipitation, similar to "Experiment 2" discussed in the '045 patent. ('045 patent at col. 4:20-54)

with and without EDTA to test for the presence of precipitation. (*Id.* at 22)

16. In their response to the court's order, defendants introduced scholarly evidence discussing the basic inverse relationship between solubility and precipitation. (D.I. 143 at 2) Defendants presented chemistry textbooks, textbooks from the pharmaceutical industry, pharmaceutical treatises, chemistry books for the layperson, and scientific journal articles. (*Id.* at 3) In addition, Dr. Myrdal discussed the inverse relationship and stated his rebuttal to plaintiffs' conclusions from the norfloxacin tests. (*Id.* at 2)

1. Plaintiffs' evidence and arguments

17. Plaintiffs argue that the norfloxacin tests show that EDTA increases the rate of precipitation, as opposed to preventing precipitation. (D.I. 144 at 10) Plaintiffs assert that the data rejects one or both of defendants' two arguments at trial that: (1) EDTA would increase the solubility of quinolones such as gatifloxacin and norfloxacin; and (2) the increased solubility would hinder quinolone precipitation. (*Id.* at 1) Because EDTA failed to prevent precipitation in the norfloxacin tests, plaintiffs argue that prevention of gatifloxacin precipitation by EDTA in the '045 patent was surprising and unknown. (*Id.* at 2-3)

18. Plaintiffs further argue that defendants' scholarly evidence is not relevant to the court's order because none of the evidence discusses quinolones, EDTA, or the effect of EDTA on solubility or precipitation. (D.I. 146 at 10) In contrast, plaintiffs assert that the norfloxacin tests answer the court's question: assuming increased solubility via EDTA, does that increase prevent the precipitation of quinolones? (*Id.* at 20) Plaintiffs

argue that the empirical and objective norfloxacin tests show that “there is no inverse relationship between increasing solubility using EDTA and decreasing precipitation of a quinolone.” (*Id.* at 5) Plaintiffs argue that the norfloxacin tests were adequate to answer the court’s question because freeze-thaw tests were relied upon by both parties and the court for both the infringement and validity analyses at trial. (*Id.* at 23)

19. At the hearing, plaintiffs presented testimony to support their finding that the effect of EDTA on the precipitation of gatifloxacin was surprising and unexpected, as evidenced by the norfloxacin test results. Plaintiffs offered testimony from: (1) inventor, Mr. Inada; (2) statistical expert, Dr. Jonathan Mahnken (“Dr. Mahnken”); (3) expert, Dr. William Curatolo (“Dr. Curatolo”) and; (4) expert, Dr. Stella.

20. The norfloxacin tests involved three rounds of experiments. (PSX-005) The tests were arguably formulated in a manner consistent with the formulation devised in the ‘456 patent. (D.I. 144 at 25) Mr. Inada, a Senju Pharmaceutical Company employee who performed the norfloxacin tests, prepared 7 pairs of formulations: 1-2; 3-4; 5-6; 7-8; 9-10; 11-12; and 13-14. (D.I. 142 at 95:24) Mr. Inada confirmed that “all samples were prepared using the same lots of the anhydrate form of norfloxacin, dihydrate form of EDTA, and trihydrate form of sodium acetate.” (*Id.* at 99:22-100:15) Mr. Inada confirmed that formulations 1-12 at varying pH levels did not dissolve at the time of preparation, therefore, only formulations 13 (without EDTA) and 14 (with EDTA) at pH 5.8 were analyzed. (*Id.* at 95:3-5; PSX-005) Formulation 13 contained 0.30g norfloxacin in 100mL of water while formulation 14 contained 0.30g of norfloxacin and 0.01g of EDTA in 100mL of water. (PSX-005 at 2)

21. In experiment 1, 5mL of each formulation was added to 10 glass ampules

and subjected to 10 freeze-thaw cycles. (*Id.*) Samples were frozen at -30°C and thawed at room temperature. (*Id.*) In experiment 2, 5mL of each solution was divided into 30 glass ampules, frozen at -30°C, and thawed at room temperature for a maximum of 10 freeze-thaw cycles. (*Id.*) In experiment 3, 5mL of each formulation was divided into 45 glass ampules, frozen at -30°C, and thawed at 25°C for a maximum of 10 freeze-thaw cycles. (*Id.* at 3)

22. Mr. Inada testified for plaintiffs that, “when freeze-thaw cycles were repeated, precipitation had occurred in all vials containing EDTA.” (D.I. 142 at 107:17-19) Mr. Inada stated that the results in each round of freeze-thaw cycles were consistent in that more samples with EDTA formed precipitate earlier compared to samples without EDTA. (*Id.* at 98:7) He also stated that samples were neither supersaturated nor saturated. (*Id.* at 105:7-9)

23. Dr. Mahnken, an assistant professor at the University of Kansas Medical Center, also testified for plaintiffs. (D.I. 106 at 141:14-15; 145:21-22) Dr. Mahnken is a statistical expert and testified with respect to the analyses he conducted using raw data from the norfloxacin tests. (D.I. 142 at 118:20-21; PSX-005) He determined whether the rate of precipitation differed in samples containing EDTA compared to those without. (D.I. 142 at 118:22-24) Dr. Mahnken’s summary report included, *inter alia*, the following statistical analyses: (1) Pearson’s chi-square analysis, testing whether samples with precipitates differ by formulation (PSX-005 at 3); (2) odds ratios, showing multiplicative measures of association (*Id.*; D.I. 142 at 146:8); (3) Kaplan-Meier survival curves generated for each formulation-by-experiment combination and overlaid for

visual inspection (PSX-005 at 4); (4) meta-analyses of combined data from all three experiments and combined data from experiments 1 and 2¹⁷ (*Id.* at 15; D.I. 142 at 121:5-7);¹⁸ and (5) confidence intervals on meta-analyses, conveying information on the precision of an estimate.¹⁹ (D.I. 142 at 122:2-144:11) Dr. Mahnken's summary report showed a faster rate of precipitate formation in samples with EDTA in all three rounds of experiments. (*Id.* at 121:10-12; PSX-005 at 15) Dr. Mahnken testified that each experiment and both meta-analyses were statistically significant.²⁰ (D.I. 142 at 120:3-121:15)

24. Dr. Curatolo, an expert in pharmaceutical formulations (including liquid pharmaceutical formulations) testified for plaintiffs regarding the propriety of the norfloxacin tests and the validity of defendants' scholarly evidence. (*Id.* at 157:11-158:3-4; 163:13-14) Dr. Curatolo testified that the norfloxacin tests were "appropriate for pharmaceutical solutions to see the effect of EDTA in preventing precipitation" and were "scientifically sound." (*Id.* at 165:10-12) Dr. Curatolo opined that the samples

¹⁷Dr. Mahnken testified that he did not conduct meta-analyses on the combined data from experiments 1 and 2 because the experimental protocol changed. (D.I. 142 at 121:20-22)

¹⁸Plaintiffs' brief states Dr. Mahnken conducted meta-analyses on experiments 1 and 2. (D.I. 146 at ¶ 10) Dr. Mahnken's summary report lists meta-analyses on experiments 2 and 3 combined. (PSX-005 at 13) Dr. Mahnken testified on direct that he conducted meta-analyses on experiments 1 and 2. (D.I. 142 at 121:5-7). Dr. Mahnken testified on cross-examination, however, that meta-analyses on combined experiments 2 and 3 were conducted. (*Id.* at 131:18-21)

¹⁹Dr. Mahnken explained, "the narrower the confidence interval the more precise an estimate, the wider the interval the less precise." (D.I. 142 at 144:11)

²⁰Dr. Mahnken testified that statistically significant levels were found at p-values less than 0.05. (D.I. 142 at 121:1-15)

were not supersaturated and it was not necessary for Mr. Inada to measure solubility because “what’s important is what goes on in freezing, not what the state of the solution was initially, in a freeze-thaw test.” (*Id.* at 163:15; 164:10-11) Dr. Curatolo stated that it was not necessary to identify or quantify the precipitate because “a freeze-thaw test is a pass/fail test,” and “the whole point is to see whether there’s a precipitate.” (*Id.* at 164:18-25; 165:2) He also agreed with Mr. Inada and Dr. Mahnken that EDTA did not increase the solubility of norfloxacin. (*Id.* at 166:19-25) With respect to the validity of defendants’ scholarly evidence, Dr. Curatolo testified that none of the evidence offered: (1) teach the use of EDTA to increase solubility; (2) teach EDTA to prevent precipitation; (3) discuss EDTA or; (4) discuss freeze-thaw testing. (*Id.* at 158:9-18) Dr. Curatolo further testified that defendants’ scholarly evidence neither discuss precipitation of quinolone pharmaceutical compositions nor discuss quinolone chemistry. (*Id.* at 158:19-24)

25. Dr. Stella, a professor of pharmaceutical chemistry at the University of Kansas testified for plaintiffs. (D.I. 107 at 225:2) It is Dr. Stella’s opinion that, “the Inada test was an appropriate test to determine if EDTA influenced precipitation in a freeze-thaw test.” (D.I. 142 at 199:25-200:3) Dr. Stella opined that freeze-thaw testing was appropriate because freeze-thaw testing was used in the ‘045 patent. (*Id.* at 194:23-24) Upon analyzing the data, Dr. Stella testified that Dr. Mahnken conducted “appropriate statistical analyses,” and that “the inverse relationship does not appear to hold true for norfloxacin.” (*Id.* at 195:20; 196:1-3) Based on the assumption that EDTA increased the solubility of norfloxacin, “one would expect Mr. Inada’s test to produce the

opposite results, for example, reduced precipitation.” (*Id.* at 231:1) Dr. Stella further testified that Dr. Myrdal’s “inverse relationship blanket statement” was “a gross oversimplification of a complex kinetic and thermodynamic event.” (*Id.* at 192:18-23) He testified that Dr. Myrdal’s statement did not take into account time or freeze-thaw cycling. (*Id.* at 192:22-23)

2. Defendants’ evidence and arguments

26. Defendants submit scholarly evidence which they assert demonstrates the inverse relationship between solubility and precipitation. (D.I. 145 at 3) For example, defendants provide two editions of a collegiate chemistry textbook²¹ that teach, “in order to predict whether a precipitate will be formed when two solutions are mixed or when a compound is added to a solution, we need to know the solubility.” (DSX-002; DSX-003) “Chemistry for Dummies” teaches that “a supersaturated solution is unstable, though, and sooner or later solute will precipitate (form a solid) until the saturation point has been reached.”²² (DSX-005) A 1991 scientific article, co-authored by plaintiffs’ expert, Dr. Stella, finds that, “if the solubility of phenytoin is increased by some mechanism in the presence of a prodrug, precipitation will be prevented which will obviously increase the precipitation times of the prodrug solutions.”²³ (DSX-007) Defendants submit other scholarly evidence which they claim further teaches the inverse relationship between

²¹RAYMOND CHANG, GENERAL CHEMISTRY: THE ESSENTIAL CONCEPTS 94-95 (3rd ed. 2003); RAYMOND CHANG, CHEMISTRY 93 (5th ed. 1994). (DSX-002; DSX-003)

²²JOHN T. MOORE, CHEMISTRY FOR DUMMIES 178 (2003). (DSX-005)

²³D.G. Muller, V.J. Stella, & A.P. Lotter, *Factors Influencing the Precipitation Time of Phenytoin in the Presence of DDM, One of its Prodrugs*, 75 INT. J. PHARM. 201-209 (1991). (DSX-007)

solubility and precipitation.²⁴

27. Along with the scholarly evidence, defendants offered testimony from Dr. Myrdal to further explain the inverse relationship. Dr. Myrdal testified that a person of ordinary skill in the art would recognize the relationship between solubility and precipitation as a “fundamental concept.” (D.I. 107 at 19:8-13) Dr. Myrdal testified that, from a basic math standpoint, equation 6 of the Brouwers reference depicted how increasing solubility decreased precipitation and conversely, as solubility decreased, precipitation increased. (D.I. 141 at 39:3-11; PSX-012 at 2559) Dr. Myrdal described mathematically how precipitation has both thermodynamic and kinetic aspects, and how both aspects are inversely related to solubility. (D.I. 141 at 58:9-19)

28. Defendants also dispute the validity of the norfloxacin tests. First, defendants argue that the norfloxacin tests do not answer the issue addressed by the court because plaintiffs’ witness, Mr. Inada, began norfloxacin testing before the court issued its November 3, 2010 memorandum order. (D.I. 143 at 5) Second, defendants argue that the norfloxacin tests were inappropriate. (D.I. 145 at 17) Defendants assert that plaintiffs’ intentions were to use the norfloxacin tests to poke holes in the teachings of the Riley reference (*Id.* at 8), however, the ratio in plaintiffs’ tests of norfloxacin to

²⁴Other evidence includes a pharmaceutical treatise that teaches, “when the solubility of a compound in water is exceeded, its solution becomes supersaturated and the compound may precipitate or crystallize.” REMINGTON’S PHARMACEUTICAL SCIENCES 274 (1985). (DSX-004)

A scientific article published in 2009 teaches, “one mechanism for inhibiting precipitation is reducing the degree of supersaturation by increasing the solubility (decrease in both nucleation and crystal growth).” Joachim Brouwers, Marcus E. Brewster, & Patrick Augistijns, *Supersaturating Drug Delivery Systems: The Answer to Solubility-Limited Oral Bioavailability?*, J. PHARM. SCI. 2549-2572 (2009) (“the Brouwers reference”). (PSX-012)

EDTA was 33:1, whereas the Riley reference teaches a 1:1 ratio. (*Id.* at 2) Defendants point to Dr. Stella's testimony that EDTA at such a low concentration "would not be expected to do anything." (D.I. 142 at 229:6-13) Thus, defendants contend that plaintiffs' norfloxacin tests were not "commensurate with the full scope of Riley's teachings, or commensurate with the full scope of claim 7, which encompasses essentially any ratio of gatifloxacin-to-EDTA and is not limited to freeze-thaw testing." (D.I. 145 at 17)

29. Defendants point to numerous other weaknesses in the norfloxacin tests. (D.I. 145 at 9) On cross-examination, Mr. Inada conceded that norfloxacin tests were not designed to evaluate the effect of solubility on precipitation. (D.I. 142 at 110:22) Mr. Inada did not measure the solubility of norfloxacin nor did he analyze whether the precipitate contained norfloxacin. (*Id.* at 108:3; 113:14) Dr. Myrdal testified for defendants that routine solubility testing, which is commonly done in the pharmaceutical industry, "defines the line between where we're going to have a precipitate and where we are not going to have a precipitate." (D.I. 141 at 29:22-30:1-3) Dr. Myrdal further testified that, in order to better understand the relationship between solubility and precipitation, pieces of data such as, "the solubility of norfloxacin at room temperature," "tests to identify exactly what the precipitate was," or "the quantity of the precipitate," are needed which were not performed in the norfloxacin tests. (*Id.* at 46:19-47:13)

30. Defendants argue that the norfloxacin tests were ineffective in challenging the court's obviousness conclusion, which is independent of freeze-thaw testing. (D.I. 145 at 4; D.I. 121 at 2) Plaintiffs conducted only freeze-thaw tests, yet claim 7 is specifically directed to aqueous liquid preparations. (D.I. 145 at 11-14; '045 patent at

col. 8:43-45) Defendants highlight that claim 7 is not limited to freeze-thaw conditions and, because defendants “showed obviousness of other embodiments within the scope of claim 7, the entire claim falls.” (D.I. 145 at 17-18; D.I. 129 at 31, n.31) (citing *Muniauction, Inc. v. Thomson Corp.*, 532 F.3d 1318, 1328 n.4 (Fed. Cir. 2008) (“claims which are broad enough to read on obvious subject matter are unpatentable even though they also read on nonobvious subject matter.”))

31. Defendants submit that the scholarly evidence proffered is relevant to the kind of chemistry in this case because claim 7 is directed to the prevention of precipitation from aqueous liquid preparations. (D.I. 145 at 10; '045 patent at col. 8:43-45) The closest prior art reference, the Riley reference, focuses on the increase of solubility in aqueous liquid compositions. (D.I. 145 at 11; JTX-015) Defendants point to plaintiffs' expert, Dr. Curatolo, who testified that the formation of precipitate in freeze-thaw tests has no bearing on whether or how precipitates form in aqueous preparations specifically called for in claim 7. (D.I. 142 at 163:1-7) In addition, plaintiffs' expert, Dr. Stella, co-authored an article premised on the basic inverse relationship between solubility and precipitation in aqueous solutions. (D.I. 145 at 11; D.I. 108 at 664:22-23) According to defendants, both the prior art and scholarly evidence are relevant while plaintiffs' evidence is legally insufficient. (D.I. 145 at 11)

32. As a final argument, defendants contend that plaintiffs are incorrect in suggesting the scholarly evidence lacks sufficiency because the evidence does not describe “quinolone, EDTA, and/or the effect of EDTA on either precipitation or solubility.” (*Id.* at 9; D.I. 146 at 10) Defendants assert that Dr. Myrdal cited the evidence, “not as proof of any explicit disclosure about EDTA or quinolones, but as

confirmation of the universal, common-sense understanding of a person of ordinary skill in the art that one way to prevent precipitation of a drug is to raise the drug's solubility." (D.I. 145 at 10; D.I. 141 at 19:3-13) Defendants cite case law explaining that, "for purposes of determining obviousness, the Court should not view each prior art reference in isolation, but rather must consider the combined teachings of the prior art references as a whole in light of the creativity and common sense of a person of ordinary skill in the art." (D.I. 145 at 9) (*quoting Duramed Pharm., Inc. v. Watson Labs., Inc.*, Civ. No. 2010-1331, 2011 WL 1086573, at *4 (Fed. Cir. Mar. 25, 2011)).

E. Applicable Law

33. "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)).

34. "[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).

35. “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)).

F. Analysis

36. In view of the reopened record, it is the court's conclusion that defendants have adduced clear and convincing evidence of the obviousness of claim 7. As a threshold matter, the court emphasizes that the parties approached the task at bar quite differently: plaintiffs tested norfloxacin (rather than gatifloxacin) and adduced data, while defendants relied on scholarly evidence, in addition to flaws in the norfloxacin tests.

37. The record shows that defendants submitted a wide range of scholarly evidence, from textbooks for the layperson with little chemistry knowledge to scientific journal articles, peer-reviewed by scientists. The court finds that this evidence sufficiently demonstrates the widely accepted, scientific principle that solubility and precipitation are inversely related.

38. Even setting aside the scholarly evidence, Dr. Myrdal's use of mathematical equations to illustrate the inverse relationship between solubility and precipitation was appropriate and persuasive. (D.I. 143 at 8) Dr. Myrdal explained that "as my solubility increases, my precipitation decreases. And conversely, then, if my solubility decreases, then my precipitation is going to increase. So that's a nice mathematical relationship to illustrate the inverse relationship between solubility and precipitation." (D.I. 141 at 39:6-11) Plaintiffs' expert, Dr. Stella, agreed. (*Id.* at 212:23-214:3)

39. Without disputing the validity of the above scientific principle,²⁵ plaintiffs

²⁵And, indeed, the inventors of the '045 patent describe this very phenomenon (without asserting its novelty) in finding that EDTA both improves the solubility of gatifloxacin ('045 patent at col. 2:13-14) and decreases the precipitation of gatifloxacin crystals. (*Id.* at col. 4:51-52)

have attempted to demonstrate that claim 7²⁶ nevertheless would not have been obvious to a person of ordinary skill based on the results of their own testing of formulations of norfloxacin (the quinolone addressed in the Riley reference) and EDTA. The court finds these tests to be irrelevant at best, unreliable at worst, as described below.

40. In the first instance, the court finds that freeze-thaw testing, as conducted by plaintiffs, was not the most appropriate way to test the relationship between precipitation and solubility. More specifically, without analysis of the identity or quantity of the precipitate and without data such as the solubility of norfloxacin at room temperature,²⁷ the norfloxacin tests are not persuasive enough to counter the general principle under scrutiny.²⁸

41. Of more concern to the court, however, is the protocol chosen for these tests. Plaintiffs' norfloxacin tests used a 33:1 ratio of norfloxacin to EDTA, a ratio inconsistent with both the ratio used in the Riley reference and that used in "Experiment 2" of the '045 patent. According to plaintiffs' own expert, Dr. Stella, EDTA at such a low

²⁶Illustrated through the freeze-thaw tests conducted in "Experiment 2" of the '045 patent, with 0.5g of gatifloxacin and 0.05g (formulation C) and 0.1g (formulation D) of EDTA. ('045 patent at col. 4:20-54)

²⁷See, e.g., D.I. 141 at 46:19-48:13; D.I. 142 at 164:18-165:2.

²⁸In this regard and contrary to plaintiffs' suggestion (*id.* at 57:16; D.I. 144 at 19), Dr. Myrdal did not testify that freeze-thaw testing was the appropriate type of test. The only reference in the record to this topic was Dr. Myrdal's discussion of another standard type of solubility test commonly performed in the pharmaceutical industry. (See D.I. 141 at 57:16-21, 28:1-30:1; D.I. 145 at 13)

concentration would not be expected to increase solubility²⁹ (or, consistent with the scientific principle under scrutiny, decrease precipitation).

42. In addition to the ratio of norfloxacin and EDTA differing from both the prior art and the '045 patent, the formulations were devised at a pH which differed from the '456 patent, which plaintiffs contend they were following. More specifically, although plaintiffs prepared 14 formulations, none were formulated at pH 5.2, used in the '456 patent. Formulations 1 and 2, having a pH at 5.3, were not evaluated. Neither were formulations 3 and 4 (pH of 6.5), 5 and 6 (pH of 7.0), 7 and 8 (pH of 7.5), 9 and 10 (pH of 5.6) or 11 and 12 (pH of 6). In summary, plaintiffs did not evaluate any formulation which did not dissolve or which did not precipitate, including formulations 1 and 2 prepared at pH 5.3, closest to the '456 patent.³⁰ Only two formulations, 13 and 14 prepared at pH 5.8, were tested. To say that the testing was selective is an understatement. And without identically mirroring either prior art reference, plaintiffs have proven nothing relevant about the obviousness of claim 7 in light of those prior art references and the knowledge of those of skill in the art.

43. Finally, the court finds Dr. Mahnken's statistical analyses unpersuasive. As noted above, it is unclear what data was used in his meta-analyses. Dr. Mahnken stated that he did not conduct meta-analysis on the combined data from experiments 1 and 2 due to a change in the experimental protocol. (D.I. 142 at 121:20-22) If this is the case, the court, then, is unsure of the reliability of the meta-analyses from combined

²⁹D.I. 108 at 604:21-606:2; D.I. 142 at 229:6-13.

³⁰See PSX-046 TR; PSX-047 TR; PSX-048 TR.

experiments 1, 2, and 3. In addition, there is nothing in the record discussing whether or not the protocol change could impact the results of the meta-analysis on combined experiments 1, 2, and 3.

III. CONCLUSION

44. For the aforementioned reasons, defendants have proven claim 7 obvious by clear and convincing evidence. 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.)
)
)
)
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ORDER

At Wilmington this 20th day of December, 2011, consistent with the opinion issued this same date;

IT IS ORDERED that the clerk of court is directed to enter judgment in favor of defendants and against plaintiffs with respect to the validity of claim 7 of U.S. Patent No. 6,333,045.


United States District Judge