IN THE UNITED STATES DISTRICT COURT FOR THE
NORTHERN DISTRICT OF WEST VIRGINIA

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U.S. DISTRICT COURT
CLARKSBURG, WV 26301

ORTHO-MCNEIL PHARMACEUTICAL, INC., JOHNSON & JOHNSON PHARMACEUTICAL RESEARCH & DEVELOPMENT, LLC, and DAIICHI PHARMACEUTICAL CO., LTD.,

Plaintiffs,

v. Civil Action No. 1:02CV32

(Judge Keeley)

MYLAN LABORATORIES, INC. and MYLAN PHARMACEUTICALS, INC.,

Defendants.

FINDINGS OF FACT AND CONCLUSIONS OF LAW

This is an action for the infringement of a chemical invention protected by U.S. Patent No. 5,053,407 (issued Oct. 1, 1991) ("the '407 patent"). The patent, entitled "Optically Active Pyridobenzoxazine Derivatives and Anti-Microbial Use," claims a compound named levofloxacin. The plaintiffs in this suit are Daiichi Pharmaceutical Co., Ltd. ("Daiichi"), levofloxacin's inventor and patent-holder, and Johnson & Johnson, the parent company of Ortho-McNeil Pharmaceutical, Inc. and Johnson & Johnson Pharmaceutical Research & Development, LLC (collectively "Ortho")[1],

[1] From time to time, the Court may also refer to the plaintiffs as "Daiichi/Ortho."

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which holds a license to distribute levofloxacin in the United States. The defendants are Mylan Laboratories, Inc. and Mylan Pharmaceuticals, Inc. (collectively "Mylan").

Mylan committed an act of infringement by filing two Abbreviated New Drug Applications ("ANDAs") (Nos. 76-276 & 77-097) with the Food and Drug Administration ("FDA"), seeking permission to manufacture and distribute a generic version of levofloxacin before the '407 patent expires. 35 U.S.C. § 271(e)(2). The ANDAs included a so-called "Paragraph IV" certification, which asserted that the '407 patent is invalid. See 21 U.S.C. § 355(j)(2)(A)(vii)(IV). As statutorily required, Mylan notified Daiichi of its ANDA filing. See id. §§ 355(j)(2)(B)(i)-(ii). In response, Daiichi and Ortho (collectively "Daiichi/Ortho") filed a timely suit for infringement on February 22, 2002. Id. § 355(j)(5)(B)(iii).

Mylan essentially concedes infringement of the '407 patent, but contends that the patent is invalid on a number of grounds. Between November 4, 2003 and December 22, 2003, the Court held a bench trial on four of these invalidity defenses--prior invention, indefiniteness, inequitable conduct and obviousness. On December 5, 2003, the Court entered judgment as a matter of law against Mylan's prior invention and indefiniteness defenses pursuant to Rule 52(c)

of Federal Rules of Civil Procedure. The Court then heard evidence on inherent anticipation, the final invalidity issue, from May 24-26, 2004. In lieu of closing arguments, the parties submitted lengthy post-trial briefs. All briefing concluded on July 12, 2004.

Pursuant to Rule 52(a) of the Federal Rules of Civil Procedure, the Court now states its findings of fact and conclusions of law.[2] As discussed below, the Court concludes that Mylan has failed to meet its burden to prove the invalidity of the '407 patent.

I. BACKGROUND OF THE INVENTION

Only claims 2 and 5 of the '407 patent are in dispute in this case.[3] Generally speaking, claim 2 is a compound claim covering levofloxacin, and claim 5 is a method claim covering the administration of "an antimicrobially effective amount" of levofloxacin to a patient.

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[2] The substance of any statement shall govern whether it is treated as a finding of fact or conclusion of law.

[3] Before trial, the Court orally dismissed all claims, affirmative defenses and counterclaims with respect to claims 1, 3, 4 and 6 of the '407 patent. Daiichi/Ortho's subsequent infringement suit (1:04CV146) as to Mylan's proposed 750mg version of levofloxacin involves the same validity issues litigated at trial, as stipulated by the parties. Thus, the two cases have been consolidated.

The invention at issue in both claims is levofloxacin, which is an enantiomeric compound. An enantiomer is one of a pair of isomers[4] that are non-superimposeable mirror images of each other. This mirror image structure is often likened to the relative structures of a person's right and left hands, and chemists normally refer to each enantiomer as either the dextro (Latin dexter, or right-handed) or levo (Latin laevus, or left-handed) enantiomer.

The right/left nomenclature also stems from the fact that enantiomers are inherently "optically active." That is, an enantiomer will rotate a plane of polarized light[5] clockwise (dextrorotatory) or counterclockwise (levorotatory). Moreover, a given pair of enantiomers will always rotate polarized light in equal and opposite directions. For example, if the dextrorotatory enantiomer rotates polarized light 90° to the right (clockwise), then the levorotatory enantiomer will rotate the polarized light 90° to the left (counterclockwise).

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[4] An isomer is one of a number of molecules that have the same chemical formula (the same constituent atoms), but the atoms are arranged in a unique pattern. For example, C_4H_{10} can be arranged as either n-butane (all carbons arranged in a chain) or isobutane (three methyl groups arranged around a central carbon atom).

[5] Polarized light is normal light that has been filtered to allow the light to shine only in one direction (normal light shines in all directions).

Because enantiomers have identical chemical formulae, chemists distinguish between the chemical names of enantiomeric pairs by preceding each with a symbol that reflects the direction the enantiomer rotates polarized light: "(+)" for dextrorotatory enantiomers, and "(-)" for levorotatory enantiomers.

Chemists also distinguish between enantiomers by designating an enantiomer as either "R" or "S" based upon the arrangement of certain atoms at the enantiomer's "chiral center."[6] Where one enantiomer is an "R," the other will be an "S."

When chemists first find or synthesize a given enantiomeric pair, the enantiomers always occur in a perfect 1:1 ratio. This solution of equal amounts of dextrorotatory and levorotatory enantiomers is known as a "racemic compound."[7] A racemic compound is optically inactive because, for every dextrorotatory enantiomer rotating polarized light to the right, there exists a levorotatory enantiomer rotating light to the left, resulting in a net rotation of zero. Chemists also have a specific nomenclature for racemic compounds - the chemical name is preceded by either "(±)" or "RS" (or both).

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[6] The chiral center is the section of an enantiomer that distinguishes it from its mate.

[7] Also referred to as a racemic mixture, or racemate.

In this case, ofloxacin is a racemic compound comprised of one dextrorotatory enantiomer with an "R" configuration and one levorotatory enantiomer with an "S" configuration. Racemic ofloxacin is disclosed in U.S. Patent No. 4,382,892 ("the '892 patent"). Levofloxacin, the subject of the '407 patent, is the levorotatory isomer of ofloxacin with the "S" configuration.

II. AMENDED CLAIM CONSTRUCTION

A. Original Claim Construction

The Court has previously construed the claims in the case at bar. See Ortho-McNeil Pharms., Inc. v. Mylan Labs., Inc., 267 F. Supp. 2d 533 (N.D. W. Va. 2003). Specifically, the Court held:

> An examination of the plain meaning of the claim language as understood by persons skilled in the art at the time of invention, the specification and the prosecution history indicate that "An S(-)-pyridobenzoxazine compound" and "S(-)-9-Fluoro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid" refer to the levorotatory enantiomer of racemic ofloxacin, levofloxacin. These terms do not refer to racemic ofloxacin. Furthermore, as demonstrated by the specification's resolution methodology, as well as the specification and prosecution history's repeated emphasis on levofloxacin's unique pharmacological properties, the disputed language refers more specifically to a pharmaceutical preparation comprised principally of levofloxacin.

Id. at 544. (emphasis added).

The Court now recognizes that its prior construction suffered from several infirmities that need to be corrected. First,

although that construction relies heavily on the specification and prosecution history, it does not explain what considerations justified their use as a source for claim limitations. Further, the Court failed to differentiate between the multiple claims at issue. Finally, the Court's perspective on the claims has been sharpened by Mylan's injection of new defenses. Accordingly, the Court finds it necessary to amend its claim construction.

B. Standard of Law

When construing patent claims, the Court must look first to the intrinsic evidence in the record: "The claims, the specification, and the prosecution history." Markman v. Westview Instruments, Inc., 52 F.3d 967, 979 (Fed. Cir. 1995) (en banc). The court does not look to each of these three sources equally; rather, they are a "hierarchy of analytical tools." Digital Biometrics, Inc. v. Identix, Inc., 149 F.3d 1335, 1344 (Fed. Cir. 1998). With these varying sources of information, the Court must be careful to always focus on interpreting the claim language as written. See Eastman Kodak Co. v. Goodyear Tire & Rubber Co., 114 F.3d 1547, 1552 (Fed. Cir. 1997) (". . . a construing court does not accord the specification, prosecution history, and other relevant evidence the same weight as the claims themselves, but

consults these sources to give the necessary context to the claim language.")

Thus, the most important part of the court's analysis is the claim language itself. See Digital Biometrics, 149 F.3d at 1344. ("The actual words of the claim are the controlling focus."); see also Johnson Worldwide Assocs., Inc. v. Zebco Corp., 175 F.3d 985, 989 (Fed. Cir. 1999) ("We begin, as with all claim interpretation analyses, with the language of the claims."). A court should interpret technical terms in claim language as having the meaning understood by persons skilled in the art, or having experience in the field at the time of invention. Hoechst Celanese Corp. v. BP Chems. Ltd., 78 F.3d 1575, 1578 (Fed. Cir. 1996).

Dictionaries have become not only a permissible source, but also a significant source, in ascertaining claim meaning. Tex. Digital Sys. v. Telegenix, Inc., 308 F.3d 1193, 1202-03 (Fed. Cir. 2002), cert. denied, 538 U.S. 1058 (2003) ("Dictionaries are always available to the court to aid in the task of determining meanings that would have been attributed by those of skill in the relevant art to any disputed terms used by the inventor in the claims."). As the Texas Digital court explained: "Dictionaries, encyclopedias and treatises, publicly available at the time the patent is issued, are objective resources that serve as reliable sources of

information on the established meanings that would have been attributed to the terms of the claims by those of skill in the art." Id. at 1202-03 (citations omitted). As with other sources of meaning, however, the dictionary definition must be disregarded if "the specification uses the words in a manner clearly inconsistent with the ordinary meaning reflected . . . in a dictionary definition." Id. at 1204 (emphasis added) (citations omitted).

Next is the specification, which the Court must consult when construing the claim language. See Markman, 52 F.3d at 979 ("Claims must be read in view of the specification, of which they are a part."); see also SciMed Life Sys., Inc. v. Advanced Cardiovascular Sys., Inc., 242 F.3d 1337, 1340-41 (Fed. Cir. 2001) (stating that it is "proper" for a district court to follow Markman's invocation); Vitronics Corp. v. Conceptronic, Inc., 90 F.3d 1576, 1582 (Fed. Cir. 1996) ("[T]he specification is always highly relevant to the claim construction analysis.")

Importantly, the Court must guard against importing limitations into the claim language from the other intrinsic and extrinsic evidence where the claim language itself does not warrant it. See Johnson Worldwide, 175 F.3d at 989-90 ("[C]laim terms cannot be narrowed by reference to the written description or

prosecution history unless the language of the claims invites reference to those sources."); Electro Med Sys., S.A. v. Cooper Life Sci., Inc., 34 F.3d 1048, 1054 (Fed. Cir. 1994) ("[C]laims are not to be interpreted by adding limitations appearing only in the specification."); SRI Int'l v. Matsushita Elec. Corp., 775 F.2d 1107, 1121 n.14 (Fed. Cir. 1985) ("Specifications teach. Claims claim.").

The third and final type of intrinsic evidence is the prosecution history. Markman, 52 F.3d at 980. The Court should consult the prosecution history to determine whether the patent applicant "consistently and clearly use[s] a term in a manner either more or less expansive than its general usage in the relevant community." ResQNet.com, Inc. v. Lansa, Inc., 346 F.3d 1374, 1378 (Fed. Cir. 2003) (citation omitted). For the prosecution history to limit the scope of the claim, however, the actions or statements that allegedly disavow a possible construction of the claim language must be "clear and unmistakable." Id. (citation omitted).

In addition to the intrinsic evidence, the Court may consult extrinsic evidence, such as expert testimony, if necessary. See Markman, 52 F.3d at 979 ("Expert testimony, including evidence of how those skilled in the art would interpret the claims, may also

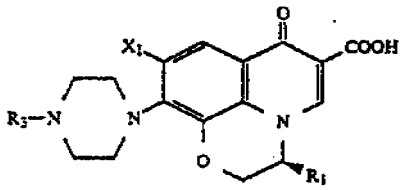
be used.") (internal quotation marks omitted). To determine what one skilled in the art could understand, the court should consider the testimony of scientific expert witnesses. See AFG Indus., Inc. v. Cardinal IG Co., 239 F.3d 1239, 1249 (Fed. Cir. 2001) (noting the value of having "scientific witnesses to aid the court in coming to a correct conclusion"); see also Key Pharms. v. Hercon Labs, Corp., 161 F.3d 709, 716 (Fed. Cir. 1999) ("[T]rial courts generally can hear expert testimony for background and education on the technology implicated by the presented claim construction issues, and trial courts have broad discretion in this regard.") Courts must be careful, however, that the expert testimony is being used only to ensure that the plain meaning is not contradicted by the understanding of one of ordinary skill in the art, not to rewrite the claim. See Voice Technologies Group v. VMC Sys., Inc., 164 F.3d 605, 614 (Fed. Cir. 1999) ("When the intrinsic evidence is unambiguous, it is improper for the court to rely on extrinsic evidence.").

When a claim term is amenable to two or more interpretations based on the applicable record evidence, it should be construed to preserve the patent's validity. Harris Corp. v. IXYS Corp., 114 F.3d 1149, 1153 (Fed. Cir. 1997); ACS Hosp. Sys., Inc. v. Montefiore Hosp., 732 F.2d 1572, 1577 (Fed. Cir. 1984).

C. Claim Construction, Revisited

1. Levofloxacin Distinguished from the Racemate

Significantly, Mylan has failed to cast doubt on the Court's key conclusion in its previous claim construction: the chemical structure referenced in claims 2 and 5, on the face of the claims, as confirmed by the specification and prosecution history, and as informed by extrinsic evidence, do not refer to racemic ofloxacin. The claims of the '407 patent that must be construed read[8]:



(VI)

1. An S(-)-pyridobenzoxazine compound represented by the formula (VI)

> wherein X1 represents a halogen atom, R1 represents an alkyl group having 1 to 4 carbon atoms, and R3 represents an alkyl group having 1 to 3 carbon atoms.
> 2. S(-)-9-Fluoro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid according to claim 1.
> 5. A process for treating a patient in need of an antimicrobial therapy in claim 4 which comprises administering to said patient an antimicrobially effective amount of S(-)-9-Fluoro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid.

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[8] Although Claim 1 is not directly at issue in this case, claims 2 and 5 depend in part on Claim 1. In particular, construction of the term "compound" is hotly contested. Claim 4 also refers to a "compound." Therefore, the term is also incorporated into Claim 5.

The parties continue to dispute the proper construction of the terms "[a]n S(-)-pyridobenzoxazine compound" and "S(-)-9-Fluoro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid."

An examination of the plain meaning of the claim language as understood by persons skilled in the art at the time of invention, the specification and the prosecution history indicates that "[a]n S(-)-pyridobenzoxazine compound" and "S(-)-9-Fluoro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid" refer to the levorotatory enantiomer of racemic ofloxacin, levofloxacin. These terms do not refer to racemic ofloxacin.

Before addressing the dispute, the Court notes that the parties agree that, to one skilled in the art, claims 2 and 5 of the '407 patent plainly refer to the "S(-)" optical isomer (enantiomer) of ofloxacin, levofloxacin.

Despite this agreement, Mylan argues that the chemical name in claims 1 and 4 needs a plain-English "purity" qualification to avoid a breadth of coverage that would include the prior art racemic ofloxacin. There are a number of problems with this position, however.

First, Mylan's argument directly conflicts with its position that the plain language of the claim refers to levofloxacin. As discussed above, chemists skilled in the art regard levorotatory enantiomers as distinct from racemic compounds or the dextrorotatory enantiomer. Additionally, each type of compound has its own unique nomenclature. "S(-)" clearly designates the levorotatory enantiomer in this case. Had the inventor meant to designate the racemic compound, he would have used the designation "(±)" or "RS." Even Mylan's own expert testified at his deposition that it "would be an error" to use only the (-) symbol to designate a racemic compound, (Jordis Dep. at 22), and a chemist would not use a lone "S" to designate a racemic compound. (Id. at 176.)

Mylan also asserts that In re Williams, 171 F.2d 319 (C.C.P.A. 1948), requires a plain-English "purity" limitation in claims for enantiomers. In Williams, the court was faced with an inventor seeking to patent an enantiomer. The claim language "call[ed] for the laevo rotary form 'substantially free from the dextro rotary form.'" Id. at 151. The Court did not construe the patent claims; indeed, aside from the preceding quotation, the claim language does not appear in the opinion at all. Thus, it is impossible to determine if the Williams court required the "substantially free" language as Mylan urges. The "substantially free" language

certainly distinguishes the levorotatory enantiomer from the racemic compound. However, there is no indication that such a plain-English purity limitation is the only way to distinguish the prior art.

The case of In re May, 574 F.2d 1082 (C.C.P.A. 1978), suggests otherwise. May, too, involved the patentability of an enantiomer. The claims at issue in that case stated:

> 1. A method of affecting analgesic and morphine antagonistic activity without producing physical dependence in animals which comprises administering to an animal an effective dosage of an acid addition salt of the levo isomer of a compound of the structure where R is a lower alkyl group and R 1 is hydrogen or a lower alkyl group.
> 2. The method of claim 1 wherein said compound is -(-)-5,9-diethyl-2'- hydroxy-2-methyl-6,7-benzomorphan.
> 3. The method of claim 1 wherein said compound is (-)-5-methyl-2'-hydroxy-2-methyl-6,7-benzomorphan.
> 4. The method of claim 1 wherein said compound is (-)-5-ethyl-2'-hydroxy-2- methyl-6,7-benzomorphan.
> 5. The method of claim 1 wherein said compound is -(-)-5-propyl-9-methyl-2'-hydroxy-2-methyl-6,7-benzomorphan.
> 6. The method of claim 1 wherein said salt is the hydrochloride.
> 7. The method of claim 6 wherein said compound is -(-)-5,9-diethyl-2'- hydroxy-2-methyl-6,7-benzomorphan.
> 8. The method of claim 6 wherein said compound is (-)-5-methyl-2'-hydroxy-2-methyl-6,7-benzomorphan.
> 9. The method of claim 6 wherein said compound is (-)-5-ethyl-2'-hydroxy-2- methyl-

> 6,7-benzomorphan.
> 10. The method of claim 6 wherein said compound is -(-)-5-propyl-9-methyl-2'-hydroxy-2-methyl-6,7-benzomorphan.
> 11. A pharmaceutical composition for internal administration having an analgesic, non-addictive, morphine-antagonistic effect which comprises a pharmaceutical carrier and an effective amount of an acid addition salt of - (-)-5,9-diethyl-2'-hydroxy-2-methyl-6,7-benzomorphan.
> 12. The composition of claim 11 wherein said salt is the hydrochloride.
> 13. The composition of claim 11 wherein said salt is the acetate.

Id. at 1084-85.

Claims 1 and 6 were rejected because they were specifically described in the prior art. Id. at 1089-90. The remaining claims were upheld. Notably, these claims contain no plain-English purity limitations whatsoever. Instead, they distinguish the enantiomer from the racemic compound with the symbol "(-)."

Mylan argues that the distinguishing language is not "(-)" but rather the phrase "without producing physical dependence in animals," which describes a chemical attribute unique to the levorotatory enantiomer. There are two problems with this analysis, however. First, the language emphasized by Mylan modifies the method for which claim 1 sought patent protection, not the compound through which that method was effected. The compound itself is simply described as "an acid addition salt of the levo

isomer of a compound [with the following structure . . . .]." Thus, the description of the compound contains no plain-English purity limitation. Most importantly, the May court stated that, under common nomenclature, a chemical compound designated as "(-)" is "limited to the levo enantiomer." 574 F.2d at 1085.

Thus, while it is certainly necessary to distinguish a new invention over the prior art, there is no indication that an inventor must use a plain-English purity limitation, as Mylan contends. Instead, an inventor may use anything that a person skilled in the relevant art would understand to limit the claim. In this case, the term "S(-)" clearly and plainly limits the claim language to the levorotatory enantiomer. Those skilled in the art clearly understand the term "S(-)" to affirmatively denote only the levorotatory enantiomer of a racemic compound, and not the racemic compound itself. Furthermore, those skilled in the art clearly understand the terms "RS" or "(±)" to affirmatively denote a racemic compound. The inclusion of "S(-)" in the claim language, coupled with the obvious exclusion of "RS" or "(±)," militates against Mylan's assertion that an additional plain-English purity limitation is necessary to distinguish the patented invention over the prior art racemic ofloxacin.

This interpretation is not contradicted by the specification or the prosecution history. Indeed, it is directly confirmed by the prosecution history. As the Court observed in its March 31, 2003, Order:

> The prosecution history is replete with instances where the inventor distinguishes levofloxacin from the prior-art racemic ofloxacin. The first three claims of the '407 patent were rejected by the patent examiner twice on the grounds that they were obvious in light of the prior art disclosure of racemic ofloxacin. Daiichi presented evidence of the differences between levofloxacin and ofloxacin until the examiner approved the patent as written.

The Court must now revisit its conclusion that the claims cover "a pharmaceutical preparation comprised principally of levofloxacin" by reviewing the language of claims 2 and 5 in light of the intrinsic record.

2. The Levofloxacin "Compound"

Claims 2 and 5, by incorporating the term from claims 1 and 4, respectively, refer to a "compound" with the structure S(-)-9-Fluoro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid. In its March 31, 2003 Order, the Court equated the term "compound" with "a pharmaceutical preparation" or drug. In reaching this conclusion the Court relied on the specification and the prosecution history, which referred to the properties of the compounds, not to confirm

this limitation, but as its source. In light of the Federal Circuit's recent decision in SmithKline Beecham v. Apotex, 365 F.3d 1306 (Fed. Cir. 2004), the Court is compelled to revisit its conclusion that claim 2, although used as a drug, has been claimed as anything more limited than a compound defined solely by chemical structure.

Mylan maintains that the word "compound" and the accompanying chemical formula comprise a broad compound claim to even a single molecule with that chemical structure. To the contrary, Daiichi/Ortho argues that claim 2 must be construed to cover more than a single molecule of ofloxacin because the specification and prosecution history contain the additional limitation that the claimed compound be pharmaceutically effective.[9] It emphasizes that a single molecule would be neither optically active nor pharmaceutically effective.

At trial, Daiichi/Ortho and Mylan presented conflicting expert testimony as to how one of ordinary skill in the art would understand the term "compound." Mylan's expert on Patent and Trademark Office ("PTO") procedures, George M. Gould, opined that

[9] In the previous claim construction, the Court identified the specific language in the specification and prosecution history that it found to support the requirement of the identified properties. The Court relies on the same language as factual support for its findings herein.

a compound claim is the broadest possible claim. (Gould Tr. at 227.) Specifically, a "compound claim is directed to the molecule itself." (Gould Tr. at 228.) This opinion was echoed by Dr. Mitscher, who stated that claim 2 "identifies a particular molecule." (Mitscher Tr. at 728.)

To the contrary, Daiichi/Ortho's expert, Dr. Klibanov, maintained that the term "compound" as used in claim 1 of the '407 patent (and as otherwise incorporated therein) indicates that the patent is not referring to a "molecule or couple of molecules sitting somewhere." (Klibanov Tr. at 1881). Under his definition of compound, the patent claim unambiguously refers to a drug: "The use of the word compound here implies that we are talking about a sizeable quantity of a material, a quantity that has certain properties, physical properties, chemical properties, and pharmacological properties." (Id.)

In support of its single molecule definition of "compound," Mylan cites multiple cases in which a compound has been construed to refer a single molecule. See, e.g., Dow Chem. Co. v. Am. Cyanamid Co., 816 F.2d 617, 618 (Fed. Cir. 1987) ("A nitrile is an organic compound containing a carbon-to-nitrogen triple bond and, depending on the rest of the molecule, can be classified as either aromatic or aliphatic"); Studiengesellschaft Kohle GmbH v. Eastman

Kodak Co., 616 F.2d 1315, 1320 (5th Cir. 1980) ("The simplest hydrocarbon molecule is a compound of one carbon atom and four hydrogen atoms and is commonly known as methane, represented by the chemical symbol CH 4.").

Most prominently, Mylan relies on the Federal Circuit's recent decision in SmithKline Beecham v. Apotex, 365 F.3d 1306 (Fed. Cir. 2004). As in the case at bar, Apotex involved a pharmaceutical patent. Engaging in a analysis similar to the one this Court followed in its prior order, the district court concluded that what appeared to be a claim defined only by chemical structure should be construed to cover only "commercially significant" quantities of that compound. Id. at 1310. On appeal, the Federal Circuit reversed this claim construction, holding that it improperly looked beyond the claim language because the "language [was] not ambiguous, but rather describe[d] a very specific compound." Id. at 1313.

Mylan further cites Schering Corp. v. Geneva Pharmaceuticals, 339 F.3d 1373, 1381 (Fed Cir. 2003), as evidence of the Federal Circuit's approach to compound claims. Although Schering involved an agreed claim construction, the unambiguous language employed by the Court suggests that the Federal Circuit will read compound claims broadly: "[C]ompound claims . . . broadly encompass

compounds defined by structure only. Such bare compound claims include within their scope the recited compounds as chemical species in any surroundings, including within the human body as metabolites of a drug." Id.

Daiichi/Ortho does not cite any case law supporting a contrary construction of the term "compound." Rather, the plaintiffs argue that, unlike the patentee in Apotex, they relied on unexpected results as the basis for establishing levofloxacin's patentability over prior art ofloxacin, and thus clearly disavowed a claim to levofloxacin that did not demonstrate those unexpected results.

Under a standard dictionary definition, "compound" means "a chemically distinct substance formed by union of two or more ingredients (as elements) in definite proportion by weight and with definite structural arrangement <water is a [compound] of oxygen and hydrogen>." Webster's Third New Int'l Dictionary 466 (2002). A "molecule" is "a unit of matter that is the smallest particle of an element or chemical combination of atoms (as a compound) capable of retaining chemical identity with the substance in mass." Id. at 1455. Therefore, Mylan's proposed definition of "compound" appears consistent with Apotex, Schering and the dictionary definition. The Court's construction of the disputed claims, however, does not end with that term.

a. Optical Activity Limitation

The Court has already concluded that "S(-)" in the claims indicates that the claimed substance is the levorotatory enantiomer. The S describes the configuration in space. The parties dispute whether the (-) in the claim language limits the claim. The Court must, therefore, determine how one of ordinary skill in the art would read the (-). Dr. Klibanov testified that the (-) indicates that the compound is "optically active," i.e., it will rotate a plane of polarized light counterclockwise. (Klibanov Tr. at 1881.) Dr. Mitscher neither disputed nor conceded that actual optical activity was required to merit the S(-) designation, but admitted that each molecule of S(-) will contribute to the optical activity of a solution of S(-) molecules. (Mitscher Tr. at 6117.)[10]

Because the parties dispute the significance of the S(-), the Court must consult a dictionary. See International Union of Pure and Applied Chemistry ("IUPAC"), Basic Terminology of Stereochemistry (IUPAC Recommendations 1996), at

[10] Mylan accuses Daiichi/Ortho of "asking the Court to impermissibly inject" the "optically active" limitation into the claims. The (-), however, is contained within the claim. The specification confirms that the claim is referring to an optically active compound by specifically employing that language; to find otherwise would be to refuse to give full effect to the language of the claim.

http://www.chem.qmul.ac.uk/iupac/stereo/NQ.html.[11] IUPAC, one of the principal authorities on stereochemistry, defines "optical activity" as follows:

> **Optical Activity**
> A sample of material able to rotate the plane of polarisation of a beam of transmitted plane-polarised light is said to possess optical activity (or to be optically active). This optical rotation is the classical distinguishing characteristic (sufficient but not necessary) of systems containing unequal amounts of corresponding enantiomers. An enantiomer causing rotation in a clockwise direction (when viewed in the direction facing the oncoming light beam) under specified conditions is called dextrorotatory and its chemical name or formula is designated by the prefix (+)-; one causing rotation in the opposite sense is laevorotatory and designated by the prefix (-)-.

Id.

This definition comports with Dr. Klibanov's testimony. According to IUPAC, "[a]n enantiomer . . . causing rotation" in a counterclockwise direction is "laevorotatory and designated by the prefix (-)-." Thus, the (-) indicates that the claims refer to an "optically active" compound.

This reading of S(-) is confirmed by the specification. The specification repeatedly refers to the invention as "optically active." '407 patent, col. 1:6-11 ("[The] invention relates to

[11] IUPAC is the International Union of Pure and Applied Chemistry. (Mitscher Tr. at 747.) Dr. Mitscher employed a definition from the same document during his trial testimony, relying on it as an authoritative source for the proper method of calculating optical purity. (Id.)

optically active pyridobenzoxazine derivatives" and "optically active compounds of Ofloxacin and its analogs"); id. at col 1:25-26 ("The present inventors obtained optically active compounds of the racemic Ofloxacin . . . ."); id. at col. 2:29-40 ("to provide optically active Ofloxacin and its analogs"; "to provide a novel intermediate . . . useful for synthesizing optically active Ofloxacin"; "to provide a novel process for preparing optically active Ofloxacin and its analogs by the use of [that] intermediate"); id. at 2:65-67 (noting three methods for preparing "optically active Ofloxacin")). Thus, the specification accords with the meaning that a person of ordinary skill in the art would have attributed to the (-) designation.

It is undisputed that more than a single molecule is required to manifest optical activity. (Klibanov. Summ. J. at 42). Not only was Dr. Klibanov's testimony on this point unimpeached and uncontradicted, but Mylan's expert, Dr. Mitscher, also admitted that a collection of levofloxacin molecules is required to exhibit optical activity, because a "single molecule would be too small" to measure its optical rotation. (Mitscher Tr. at 991.) Thus, on their face, the claims require at least enough levofloxacin molecules to rotate polarized light.

b. Purity Limitation

The claims do not expressly refer to a specific minimum optical purity or percentage of the detrorotatory enantiomer. In its prior claim construction, however, the Court described the claims as covering something "comprised principally of levofloxacin." That terminology gave rise to significant debate during trial. The language, however, was intended to capture a concept that was only reinforced at trial: a person of ordinary skill in the art at the time of the filing of the '407 patent would have understood the claim to cover levofloxacin with a purity that was highly, but less than 100 percent, optically pure. The Court did not reference a minimum purity because no minimum purity was claimed or identified in the intrinsic record.

To determine what one skilled in the art could understand, the court should consider the testimony of scientific expert witnesses. See AFG Indus., Inc. v. Cardinal IG Co., 239 F.3d 1239, 1249 (Fed. Cir. 2001). The Court is dealing here with highly technical terms. Therefore, it must rely on the education it received from the experts as to whether one of ordinary skill in the art would have read the reference as referring to a 100 percent pure substance.

Because of the nature of enantiomeric separation at the time, one of ordinary skill in the art would not have read a claim to an enantiomer of ofloxacin as requiring 100 percent purity. Dr. Klibanov testified that when chemists refer to 100 percent purity they understand that "there is always that molecule hiding somewhere in the corner. There is no such thing as an absolutely 100 percent .0000 pure substance." (Klibanov Tr. at 1899.) Mylan's expert, Dr. Mitscher, implicitly conceded this when he calculated the optical purity of Example 6. He "arbitrarily" treated Example 7 as 100 percent pure, recognizing that it "may, in fact, not be 100 percent [pure]," but it was "the purest sample available" in the '407 patent. (Mitscher Tr. at 741-42.) Further, Mitscher stated that the purity number he would require was "very high, 100 percent if possible, but you know as pure as can reasonably be obtained for a product at this time." (Mitscher Tr. at 932.)

Thus, although one of ordinary skill in the art would have understood the claim to the compound levofloxacin to be substantially pure levofloxacin, the realities of science would have led such a skilled artisan to conclude that the purity was not 100 percent. This is confirmed by the specification, particularly in the examples. As Drs. Klibanov and Mitscher testified, not all

of the examples, and perhaps none of the examples, yielded 100 percent pure levofloxacin. Therefore, the Court declines to adopt such a limitation and construes claim 2 of the '407 patent to cover substantially pure levofloxacin.

3. Construction Issues Unique to Claim 5

Claim 5 provides more description than the chemical structure described in claim 2. It is a claim to a method of administering levofloxacin. At issue is whether the language in the claim limits the claim in any other respect.

The language "administering to said patient an antimicrobially effective amount" of levofloxacin could be read to provide a quantity limitation. Specifically, it could limit the claim to levofloxacin in quantities that are antimicrobially effective.

The Federal Circuit was presented with a similar claim construction issue in Key Pharmaceuticals v. Hercon Laboratories Corp., 161 F.3d 709 (Fed Cir. 1998), which involved the construction of the term "pharmaceutically effective amount" in a patent for a patch that delivered nitroglycerin through the skin. It affirmed the district court's use of extrinsic evidence, in the form of FDA ranges for the required quantity, to place a numerical value on "pharmaceutically effective." Although the parties in that case disputed how much nitroglycerine would constitute a

"pharmaceutically effective" amount, there was no suggestion that the term did not limit the claim at issue. Applying that implied principle to the case at bar, the Court finds that the term "antimicrobially effective" limits the claim by requiring enough levofloxacin molecules to exhibit antimicrobial activity.

Further, claim 5 discusses "administering" the levofloxacin. Daiichi/Ortho maintains that this term limits the claim to something delivered from outside the body and thereby excludes in vivo production of levofloxacin. In response, Mylan argues that if ofloxacin were to become levofloxacin in vivo, an antimicrobially effective amount of levofloxacin would have been administered when ofloxacin was administered. It therefore maintains that the language does not exclude in vivo production.

Mylan's construction is supported by the Merriam Webster Medical Dictionary's definition of administer, "to give remedially (as medicine)." Whether levofloxacin formed as the claimed compound inside the body or outside the body, as long as it is given remedially as medicine, then levofloxacin has been administered. Thus, claim 5 does not contain a preingestion limitation.

4. Claims Construed

Claim 2 refers to a compound comprised of an optically active and substantially pure quantity of levofloxacin. Claim 5 is a method of administering an antimicrobially effective amount of the compound identified in claim 2.

III. JUDGMENTS AS A MATTER OF LAW

At the close of Mylan's case-in-chief, Daiichi/Ortho moved for judgment on partial findings pursuant to Federal Rule of Civil Procedure 52(c). Rule 52(c) provides:

> If during a trial without a jury a party has been fully heard on an issue and the court finds against the party on that issue, the court may enter judgment as a matter of law against that party with respect to a claim or defense that cannot under the controlling law be maintained or defeated without a favorable finding on that issue . . . .

The rule further requires that the judgment shall be supported by findings of fact and conclusions of law. Id. The Court granted Daiichi/Ortho's Rule 52(c) motion as to Mylan's prior invention and indefiniteness defenses, making oral findings of fact and conclusions of law. The Court now issues written findings so that the record on appeal is clear.

A. Prior Invention

1. Standard of Law

Invalidity based on prior invention is a question of law that must be proven by clear and convincing evidence. Gambro Lundia AB v. Baxter Healthcare Corp., 110 F.3d 1573, 1576 (Fed. Cir. 1997). Under the patent laws, a person shall be entitled to a patent unless:

> [B]efore such person's invention thereof, the invention was made in this country by another inventor who had not abandoned, suppressed, or concealed it. In determining priority of invention . . . there shall be considered not only the respective dates of conception and reduction to practice of the invention, but the reasonable diligence of one who was the first to conceive and last to reduce to practice, from a time prior to conception by the other.

35 U.S.C. § 102(g)(2).

Ordinarily, under United States patent law, it is the date of conception, not the filing date or the date of the actual production of the invention, that establishes the invention date. Scott v. Koyama, 281 F.3d 1243, 1245-46 (Fed. Cir 2002); Fina Oil and Chem. Co., 123 F.3d 1466, 1473 (Fed. Cir. 1997). Conception alone, however, is not sufficient to prevail on the defense of prior invention; subsequent diligent reduction to practice must also be proven. Price v. Symsek, 988 F.2d 1187, 1190 (Fed. Cir. 1993). This framework applies only to inventions conceived in the United States. See 35 U.S.C. § 102(g)(2).

When an invention was not conceived in the United States, but is the subject of an earlier-filed foreign patent application, the applicant may claim a priority date of the foreign application if the foreign application meets certain requirements. Tronzo v. Biomet, Inc., 156 F.3d 1154, 1158 (Fed. Cir. 1998). Nonetheless, applicants with a foreign patent may only receive credit for activities performed outside the United States that were included in a patent application. Scott, 281 F.3d at 1246 n.2.

Reliance on a foreign application's date is a "constructive reduction to practice." 35 U.S.C. § 104. Because a foreign patent holder does not receive recognition for conception, however, it will lose a priority contest if another party can prove conception in the United States before the filing date of the foreign patent. See id. at 1242. This is true even if the inventor in the United States does not succeed in reducing the invention to practice until after the foreign filing date, as long as he or she can prove diligence and ultimate success in a reduction to practice. See id.

2. Findings of Fact and Conclusions of Law

a. The Japanese Patents

The '407 patent application was filed with the PTO on June 5, 1986. One year before that filing in the United States, Daiichi filed the first of three Japanese patent applications, which, taken

together, comprise the '407 patent application. Each subsequent application disclosed a new process for making levofloxacin. These processes are referred to in the '407 patent as Processes A, B, and C.

Daiichi filed its first patent application claiming levofloxacin, Japanese Patent Application No. 60-134712 (the "'712 application"), in Japan on June 20, 1985. (PX 981.) That application disclosed Process A, which describes the synthesis of levofloxacin by resolving an intermediate column that Daiichi had produced using a High Performance Liquid Chromatography ("HPLC") column. Process A was limited in that it did not allow for the production of large quantitities of levofloxacin. The levofloxacin produced by Process A was also less pure than that produced by the later-developed processes. Process A corresponds to Example 6, which is identical in the '712 and '407 patent applications. (DX 1 at col. 14, lines 6-45; DX 8 at 315-16.)

The second Japanese patent application for levofloxacin, No. 30-2226499 (the "'499 application"), filed on October 11, 1985, disclosed Process B, which involved the production of levofloxacin using the lipase enzyme from Pseudomonas aeruginosa. This process allowed for the production of greater quantities of levofloxacin,

which, in turn, provided the opportunity for more significant analysis and testing of the drug.

The third Japanese application, filed on January 28, 1986, disclosed Process C. Process C was adapted from a process devised by Dr. John F. Gerster and presented at a September 1985 conference sponsored by the Interscience Conference on Antimicrobial Agents and Chemotherapy ("ICAAC"). Gerster's work did not involve levofloxacin, but another fluoroquinolone called flumequine. Process C involves the use of L-tosyl proline as a reagent and allows for production of greater quantities of levofloxacin than either Process A or Process B. All three processes were included in the '407 patent application.

The '407 patent included a total of seventeen (17) examples describing the production of levofloxacin and its intermediates, and covering three distinct processes. (DX 1.) On December 9, 1986, Bayer AG, another pharmaceutical company, submitted a patent application for levofloxacin. (DX 11.) Although that application went through a separate patent prosecution process, the PTO ultimately found that both patent applications were allowable. (Id.) Therefore, in June 1989, the PTO declared an interference proceeding to determine which party had priority, with the Daiichi

applicants being declared the senior party and the Bayer AG applicants the junior party. (DX 8 at 276-80.)

In connection with the interference proceeding, the Daiichi parties submitted a preliminary motion "to be Accorded Benefit of its Japanese Priority Applications." (DX 17.148.) The Bayer AG parties opposed this motion on the ground that the Japanese applications did not disclose the entire subject matter of the '407 patent. (DX 17.216.) In February 1991, the PTO's Board of Patent Appeals and Interferences granted Daiichi's motion over Bayer's objection, and Daiichi was given the benefit of the priority date of its first Japanese patent application, June 20, 1985. (DX 17.414-19.)

b. Mylan's Claims

Mylan's case on prior invention had two essential components, both of which it needed to prove in order to prevail. First, Mylan challenged Daiichi's June 20, 1985 priority date, claiming that the priority date should be October 11, 1985, the date of its second patent application containing Process B. Second, it identified an alleged prior invention of levofloxacin in September 1985 by its expert, Dr. Mitscher, along with Dr. Daniel Chu, a scientist then employed by Abbott Laboratories. If proven, that September 1985

invention would have pre-dated Daiichi's second Japanese patent application by one month.

For its prior invention defense, Mylan bore the burden of establishing in its case-in-chief, by clear and convincing evidence, that (1) the '712 patent application did not cover levofloxacin as claimed in the '407 patent, and (2) Mitscher and Chu conceived of levofloxacin as claimed in the '407 patent in mid-September 1985 and, therefore, diligently reduced that invention to practice.

i. Entitlement to the June 20, 1985 Priority Date

Mylan maintains that Daiichi is not entitled to priority based on the filing of the '712 application because it did not sufficiently describe levofloxacin. Specifically, Mylan contends that Example 6, which describes Process A and is also present in the specification of the '407 patent, does not produce levofloxacin as claimed in the '407 patent. (DX 1 at cols. 3-4; Mitcher Tr. at 627-28.) Not only is the content of Example 6 identical in the '712 and '407 patents, but the MIC,[12] or potency, data for

[12] MIC stands for "minimum inhibitory concentration," and refers to the activity of an antimicrobial agent against a particular pathogen. A lower MIC indicates higher potency. (Mitscher Tr. at 514-15.)

levofloxacin and ofloxacin remained constant from the '712 application to the '407 application. (Mitscher Tr. at 911-12.)

For an inventor to claim priority based on the filing date of a foreign patent application, the earlier application, also known as the "parent," must reasonably convey to one of skill in the art that the inventor possessed the later-claimed subject matter at the time the parent application was filed. Tronzo, 156 F.3d at 1158. Because it fulfills the written description requirement typically embodied by the specification, the disclosure must describe the claimed invention with all its limitations. Id. (observing that the written description requirement is a statutory mandate under 35 U.S.C. § 112).

Whether a parent application sufficiently describes the invention is a highly fact-specific inquiry. See Vas-Cath Inc. v. Mahurkar, 935 F.2d 1555, 1562 (Fed. Cir. 1991); Ralston Purina Co. v. Far-Mar-Co, Inc., 772 F.2d 1570, 1575 (Fed. Cir. 1985). Although "a disclosure in a parent application that merely renders the later-claimed invention obvious is not sufficient to meet the written description requirement," Tronzo, 156 F.3d at 1158, a claim may be broader than the specific embodiment disclosed in the parent application's specification. Ralston Purina, 772 F.2d at 1562. (citation omitted).

Mylan does not assert that Example 6 failed to reasonably convey to a skilled artisan that the inventor possessed the compound yielded in that example. Instead, Mylan argues that Example 6 did not disclose a compound pure enough to be considered levofloxacin as claimed in the '407 patent and embodied in examples yielding levofloxacin of greater optical purity. Mylan's real argument appears to be that the foreign patent must be limited to whatever embodiment of the invention the inventor was capable of reducing to practice at the time the foreign patent was filed. That, however, is not the law. The error in Mylan's position is illustrated by examining the facts of Tronzo, the case on which Mylan principally relies.

In Tronzo, the Federal Circuit denied a foreign patentee the priority date from its parent application. 156 F.3d at 1159. The case involved technology related to artificial hip sockets that included cup implants adapted for insertion into the hip bone. Id. at 1156. The parent application had described only conical cups, while the later United States patent application claimed hemispherical cups. Id. at 1159. The foreign patent holder maintained, however, that the foreign patent application had described a sufficient number of cups to generically claim them. Id. The Federal Circuit found this assertion unsupportable because

the foreign application had emphasized the conical shape as "extremely important," and only discussed other cups to distinguish the conical ones as superior to the prior art. Id. Thus, the foreign application contained no reference to the later-claimed hemispherical cups and specifically limited the invention to conical cups.

The facts in the case at bar differ significantly from those in Tronzo. There, the court denied the patent applicant the benefit of the foreign priority date because the new application claimed a different invention from what had been claimed in the parent application. Here, the difference between Example 6 and the later-developed, more highly pure embodiments of levofloxacin in the '407 patent, is a difference of degree, not kind. It is clear from examining the claim and specification in the '712 patent application that the inventors isolated the levorotatory enantiomer, and that they did so to gain the benefit of the isomer's relatively superior properties and inform skilled artisans how to practice the claimed invention. It was not a claim to Process A itself, but to its product. Although Mylan suggests otherwise, the fact that additional processes for producing the claimed invention were included in the '407 patent does not negate Daiichi's claim to the invention as of the filing of the '712 application.

Mylan further argues that Example 6 is not within the scope of the '407 patent because it does not produce levofloxacin with optical purity of "approximately ninety-five percent or better" based on the enantiomeric excess method of calculating optical purity. According to Mylan, "approximately ninety-five percent" is the purity floor established in the summary judgment testimony of Daiichi's expert, Dr. Klibanov. (Klibanov Summ. J. at 44.)

There are two different methods for measuring an enantiomer's optical purity, the percentage method that Dr. Klibanov employed in obtaining the 95 percent figure, and the enantiomeric excess method employed by Mylan's expert, Dr. Mitscher. Both values represent the ratio of the majority enantiomer to the minority enantiomer. In fact, to convert from the value under the percentage method to the value under the enantiomeric excess method, one need only perform an additional subtraction to exclude the presence of the dextrorotatory enantiomer.[13] (Mitscher Tr. at 902-03.) Although Mitscher maintains that the enantiomeric excess method is the only valid method for calculating for optical purity, he does not deny

[13] Thus, whereas Klibanov asserts that the optical purity of Example 6 is .9366 or 93.66% levorotatory enantiomer and .0634 or 6.34% dextrorotatory enantiomer, Mitscher maintains that the proper process is to again subtract out the percentage of the dextrorotatory enantiomer because one is only concerned with the levorotatory enantiomer. Subtracting an additional .0634 from the .9366 yields Mitscher's number for optical purity .873 or 87.3%. (Mitscher Tr. at 747-49.)

the mathematical relationship between that method and the percentage method.

For purposes of deciding the prior invention issue the Court need not determine which method utilized by the experts is superior. What matters is that Drs. Klibanov and Mitscher employed different methods that yielded different results.

Klibanov arrived at his optical purity estimation by calculating the optical purity of the least pure example in the '407 patent (Example 6) using the percentage method. Because claims are typically read to cover the examples, he concluded that the optical purity of the least pure example was the lowest covered by the '407 patent.

Using the enantiomeric excess formula for determining optical purity, Mitscher concluded that the minimum optical purity of levofloxacin in the '407 patent is 87.3% Therefore, he argued that Example 6 fails to meet the minimum purity level proffered by Klibanov, i.e., "approximately ninety-five percent or better." Mitscher's conclusion, however, is plainly erroneous because it compares Klibanov's baseline purity estimation from Example 6, calculated by the percentage method, with a purity estimation of the same example calculated by the enantiomeric excess method. To make a proper comparison, both purity estimations must be calculated by the same formula. When converted accordingly (using

either method), the purity estimations of both experts are equal. Thus, Mitcher's opinion is illogical because it implies that, depending on the formula used, Example 6 can be less optically pure than the least optically pure example in the patent, which is also Example 6.

Mitscher also does not fully embrace Klibanov's assertion that the claims cover the examples. Although Klibanov and Mitscher agree that one of ordinary skill would normally look to the examples as a source of the optical purity limitation, Mitscher testified that the examples do not provide an optical purity limitation in the case at bar because of the language in the patent that the examples are not intended to limit the claims. (Klibanov Summ. J. at 43-44; Mitscher Tr. at 729-30, 914.) On that theory, however, Mitscher's attempt to isolate Example 6 to determine optical purity is unavailing because that example is situated no differently than the other examples. Therefore, Mylan fails to prove by clear and convincing evidence that Daiichi's parent application failed to sufficiently describe levofloxacin. As such, the June 20, 1985 priority date stands.

ii. Alleged Prior Invention By Mitscher and Chu

Even if Daiichi's priority date rested solely on its '499 application, filed on October 11, 1985, Mylan still bore the burden

at trial of proving conception by another inventor prior to that date.

Conception requires that the inventor have "a specific, settled idea, a particular solution to the problem at hand, not just a general goal or research plan he hopes to pursue." Burroughs Wellcome Co. v. Barr Labs., Inc., 40 F.3d 1223, 1228 (Fed. Cir. 1994). It is only complete when the inventor has a reasonable expectation that he or she will produce the claimed invention. Hitzeman v. Rutter, 243 F.3d 1345, 1358 (Fed Cir. 2001). Further, its contours must be "so clearly defined in the inventor's mind that only ordinary skill would be necessary to reduce the invention to practice, without extensive research or experimentation." Burroughs Wellcome, 40 F.3d at 1228.

Conception is a question of law based on underlying factual findings. See Gambro Lundia AB v. Baxter Healthcare Corp., 110 F.3d 1573, 1576 (Fed. Cir. 1997). It must be proven by clear and convincing evidence. See id. To satisfy this burden, inventors cannot prove conception through their own testimony alone. Trovan, Ltd. v. Sokymat SA, Irori, 299 F.3d 1292, 1302 (Fed. Cir. 2002) (citing Price v. Symsek, 988 F.2d 1187, 1194 (Fed. Cir. 1993)). Corroboration is required regardless of the inventor's level of interest in the litigation. Finnigan Corp. v. Int'l Trade Comm'n, 180 F.3d 1354, 1369 (Fed. Cir. 1999).

"Whether the inventor's testimony has been sufficiently corroborated is evaluated under a 'rule of reason' analysis." Trovan, 299 F.3d at 1302. Under this analysis, courts evaluate "all pertinent evidence . . . so that a sound determination of the credibility of the [alleged] inventor's story may be reached." Id. Factors to be considered in this analysis include:

> (1) delay between event and trial, (2) interest of witness, (3) contradiction or impeachment, (4) corroboration, (5) witnesses' familiarity with details of alleged prior structure, (6) improbability of prior use considering state of the art, (7) impact of the invention on the industry, and (8) relationship between witness and alleged prior user.

Juicy Whip, Inc. v. Orange Bang, Inc., 292 F.3d 728, 741 (Fed. Cir. 2002). Although circumstantial evidence may be used to corroborate a claimed conception, physical records created contemporaneously with the alleged prior invention are preferred. See Trovan, 299 F.3d at 1303.

Mylan asserts that its expert, Dr. Mitscher, together with Dr. Chu, a scientist then employed by Abbott Laboratories ("Abbott"), conceived of levofloxacin in September 1985. (Mitscher. Tr. at 755-56.) The evidence in support of this assertion was derived from the file in a PTO interference between Mitscher and scientists from Bayer, interference No. 102,548 (the "Mitscher-Bayer Interference"), and includes most prominently an affidavit executed

by Mitscher on January 31, 1992 expressly for that proceeding. (DX 16.)

Mitscher testified that he and Chu conceived of levofloxacin during a meeting between the two on or about September 18, 1985. (Mitscher Tr. at 762-63.) Pages from Mitscher's calendar reflecting that he was at Abbott during those days are the sole evidence of this meeting. (Mitscher Tr. at 764-65) No third party was present at the meeting, which Mitscher conceded was preliminary in nature. (Mitscher Tr. at 764, 934.)

Attached to Mitscher's 1992 affidavit was a document entitled "Confidential Memorandum of Invention," authored by Chu and received at Abbott's internal patent office on September 27, 1985. (DX 16.84; Mitscher Tr. at 765-66.) The Confidential Memorandum reports that Mitscher and Chu invented a novel method of producing the racemate and enantiomers of ofloxacin. (DX 16.) Although Mitscher testified that he and Chu had sketched a rough schematic during their September meeting that he believed Chu would have attached to the Confidential Memorandum, there is no documentary description of this alleged schematic attached to the existing copy of the Confidential Memorandum or in any other record. (Mitscher Tr. at 936-39.) Nor did Mitscher or any other witness testify from personal knowledge that there was ever any schematic attached to the Confidential Memorandum. Mitscher played no role in drafting

the Confidential Memorandum, although he stated that he later viewed it in conjunction with the Mitscher-Bayer interference, and he has never seen it with any attachment. (Mitscher Tr. at 936-37).

The oldest surviving written record containing any portion of the schematic that Mitscher claims he and Chu conceived in September 1985 is contained in the first entry of the laboratory notebook of Dr. Padam Sharma, a scientist working under Mitscher, made on December 25, 1985. (Mitscher Tr. at 937-38.) That entry, however, does not contain the entire schematic that Mitscher claims he and Chu devised. (Mitscher Tr. 938.) The schematic is not described fully until entries in Sharma's notebook that are dated sometime after December 1985. (Id.)

Indeed, there is no corroborated evidence at all that Mitscher, or anyone working with him or under his direction, ever made levofloxacin. The compound reflected in Sharma's notebook in February 1986, PO-7, was a difluoro precursor, not levofloxacin, and none of the existing spectra analyzing it remains. (Mitscher Tr. at 955, 968-69.) Although Mitscher claims to have successfully made levofloxacin in March 1986, he admits that he never measured its optical rotation, nor does he have any existing data supporting this claim. (Mitscher Tr. at 952-56.) On April 25, 1986, Mitscher filed patent application number 4,777,253 (the "'253 patent"),

which purported to claim a process for making levofloxacin, but that application did not provide any physical data or optical rotation information. (DX 28.)

Mitscher testified that the schematic in his affidavit from the Mitscher-Bayer interference is a reproduction of the invention as it existed in September 1985. He further stated that one of ordinary skill could have reduced the invention to practice based on the schematic "using routine laboratory operations." (Mitscher Tr. at 1225-26.) Thus, were the Court to credit Mitscher's testimony in its totality, and find that testimony alone sufficient to satisfy Mylan's burden, Mylan may have established conception.

The Court, however, cannot give full credit to Mitscher's testimony. As a rival inventor and an expert witness for Mylan, he clearly has some interest in the outcome of this litigation. More significantly, the Court has good reason to question the clarity of his memory in light of the fact that his testimony focused on a single meeting that took place eighteen (18) years before he testified. Thus, the rule that corroboration is required is especially forceful in the case at bar.

At trial, Mylan offered the following as evidence of corroboration: Mitscher's calendar pages, Chu's Confidential Memorandum, Sharma's laboratory notebook, and affidavits of Mitscher, Chu, and Sharma from the Mitscher-Bayer interference.

Mylan's corroboration is lacking, however, because none of those documents is sufficient, either viewed alone or together, to corroborate invention in September 1985. The documents created in September 1985 do not provide sufficient detail for the Court to determine that Mitscher and Chu had anything beyond a general goal or research plan. The calendar pages do not even reference the subject matter of the meeting. Although the Confidential Memorandum reports that Mitscher and Chu invented a novel method of producing the racemate and enantiomers of ofloxacin, it does not contain the schematic Mitscher claims to be his invention or provide any further detail. According to Mitscher, the schematic was originally attached to the Confidential Memorandum, but he admits that he never saw the Confidential Memorandum with any attachment. The Sharma notebook may corroborate an invention, but not one produced before October 11, 1985. The notebook contains no evidence of work done on the invention before November 25, 1985, the date of the first entry. Further, the notebook does not refer to a September date of conception. Accordingly, while the notebook may corroborate a later conception or reduction to practice, it does not corroborate a September date. As Mitscher admitted, there is no existing documentary evidence of the purported invention between October 1, 1985 and November 24, 1985.

Although documentary evidence is not required, some type of independent corroboration is.

Finally, the Mitscher and Chu interference does not corroborate the September 1985 date. The affidavits are statements by the inventors, and, thus, they require independent corroboration. Although Mitscher and Chu had assigned their patent rights to Abbott, their affidavits lack reliability because they were executed seven years after the claimed invention, when Mitcher's and Chu's memories as to the events may have been faulty. Their reliability is further undermined by the context in which they were executed. The affidavits were created to support Abbott's priority claim in the Mitscher-Bayer interference. Although they had assigned their rights, Mitscher and Chu still had an inherent interest in prevailing in the interference because of the credit they would receive as inventors. Accordingly, the affidavits are not sufficiently reliable to corroborate Mitscher's testimony.

Therefore, applying a rule of reason analysis, the delay between the event and trial, the interest of the witness, the lack of corroboration, and the relationship between the witness and the alleged prior user all weigh against a determination that Mitscher's testimony has been sufficiently corroborated. Accordingly, the Court cannot find by clear and convincing evidence

that Mitscher and Chu conceived of levofloxacin before October 11, 2004.

c. Conclusion

For the foregoing reasons, Mylan failed to present sufficient evidence in its case-in-chief to sustain its burden of proving that Daiichi was not entitled to the priority date of June 20, 1985, or that Drs. Mitscher and Chu conceived of levofloxacin in September 1985. Therefore, the Court granted Daiichi/Ortho's motion for partial judgment on Mylan's prior invention defense.

B. Indefiniteness

1. Standard of Law

"[D]etermination of claim indefiniteness is a legal conclusion that is drawn from the court's performance of its duty as the construer of patent claims." Exxon Research and Eng'g Co. v. United States, 265 F.3d 1371, 1376 (Fed. Cir. 2001). "A claim is indefinite [under 35 U.S.C. § 112, ¶ 2,] if, when read in light of the specification, it does not reasonably apprise those skilled in the art of the scope of the invention." Amgen Inc. v. Hoechst Marion Roussel, 314 F.3d 1313, 1342 (Fed. Cir. 2003). "If the meaning of the claim is discernible, even though the task may be formidable and the conclusion may be one over which reasonable persons will disagree, [the Federal Circuit has] held the claim sufficiently clear to avoid invalidity on indefiniteness grounds."

Exxon Research and Eng'g, 265 F.3d at 1375 (citing Modine Mfg. Co. v. U.S. Int'l Trade Comm'n, 75 F.3d 1545, 1557 (Fed. Cir. 1996), and Athletic Alternatives, Inc. v. Prince Mfg., Inc., 73 F.3d 1573, 1581 (Fed. Cir. 1996)).

"The standard of indefiniteness is somewhat high; a claim is not indefinite merely because its scope is not ascertainable from the face of the claims. Rather, a claim is indefinite under § 112 if it is insolubly ambiguous, and no narrowing construction can properly be adopted." Amgen, 314 F.3d at 1342 (citing LNP Eng'g Plastics, Inc. v. Miller Waste Mills, Inc., 275 F.3d 1347, 1359-60 (Fed. Cir. 2001)). "By finding claims indefinite only if reasonable efforts at claim construction prove futile, [the court] accord[s] respect to the statutory presumption of patent validity, and [it] protect[s] the inventive contribution of patentees, even when the drafting of their patents has been less than ideal." Exxon Research and Eng'g, 265 F.3d at 1375 (citation omitted).

2. Findings of Fact and Conclusions of Law

Mylan contends that the lack of an explicit optical purity value for the claimed compound renders claims 2 and 5 indefinite. As discussed in the amended claim construction, however, such a limitation is neither a legal requirement nor a practical necessity to adequately convey the scope of the invention at issue here.

Mylan otherwise fails to persuade the Court that the patent is "insoluably ambiguous." Although the parties' experts disagreed about precise optical purity calculations, Mylan did not solicit any testimony suggesting that persons skilled in the relevant art could not discern the scope of the levofloxacin claims. To the contrary, Dr. Mitscher's proposed calculation of optical purity illustrates that the claims are amenable to construction. (Mitscher Tr. at 731, 744, 751.) Therefore, the Court granted Daiichi/Ortho's motion for judgment as a matter of law with respect to Mylan's indefiniteness defense.

IV. POST-TRIAL JUDGMENTS

A. Inequitable Conduct

1. Standard of Law

Inequitable conduct includes affirmative misrepresentation of a material fact, failure to disclose material information, or submission of false material information, coupled with an intent to deceive by a person with a duty of candor. Bd. of Educ. ex rel. Bd. of Trs. of Fla. State Univ. v. Am. Bioscience, Inc., 333 F.3d 1330, 1343 (Fed. Cir. 2003). The duty of candor applies only to the attorneys who prosecute patents and the inventors.

First, the trial court must determine whether the conduct meets a threshold level of materiality and intent to mislead the PTO. Id. Intent to deceive may be inferred, and the court is more

likely to infer intent to deceive as the materiality of a fact increases. Abbott Labs. v. TorPharm, Inc., 300 F.3d 1367, 1380 (Fed. Cir. 2002). Intent and materiality are questions of fact which must be proven by clear and convincing evidence. Dayco Prods., Inc. v. Total Containment, Inc., 329 F.3d 1358, 1362 (Fed. Cir. 2003). Once the threshold levels of materiality and intent have been established, the trial court is required to weigh them to determine whether the applicant's conduct is so culpable that the patent should be held unenforceable. Am. BioScience, Inc., 333 F.3d at 1343.

2. Findings of Fact and Conclusions of Law

As a preliminary matter, Daiichi/Ortho has urged the Court to ignore a number of the alleged representations and omissions. First, it maintains that, although Daiichi sought the patent based on asserted unanticipated advantages over ofloxacin as to the properties of potency, toxicity, and solubility, the patent was not granted on that basis, as the prosecution of the rival Bayer application illustrated. The inequitable conduct inquiry is not, however, a "but for" standard. Merck & Co. v. Danbury Pharm., Inc., 873 F.2d 1418, 1421 (Fed. Cir. 1989). Moreover, because the Examiner never stated his reasons for allowing the patent, Daiichi's arguments with respect to levofloxacin's properties cannot be disregarded.

Second, Daiichi/Ortho relies on the case of CFMT, Inc. v. YieldUp Int'l Corp., 349 F.3d 1339 (Fed. Cir. 2003), to contend that the attorney argument in the requests for reconsideration cannot serve as a basis for a finding of inequitable conduct. The Court does not read CFMT so broadly, however. That case concerned attorney argument on unexpected results that involved "bare statements without objective evidentiary support," as well as clear evidence in the record that the Examiner did not rely on unexpected results. Id. at 1342. In contrast, the attorney advocacy during the prosecution history of the '407 patent relied on factual data, and the Court cannot be certain whether that advocacy was a factor in the Examiner's decision to allow the patent.

Mylan alleges that Daiichi engaged in four instances of inequitable conduct, each of which, if proven, would require invalidation of the '407 patent. Three of the allegedly inequitable acts and omissions relate to the purportedly unanticipated properties of levofloxacin: toxicity, solubility, and potency. The other allegation of inequitable conduct concerns the failure to disclose the so-called 1985 Gerster reference, which pertains to Daiichi's duty to disclose prior art.

a. Toxicity Tests

Mylan maintains that Daiichi acted inequitably by submitting statistically insignificant toxicity data indicating that

levofloxacin was less toxic than ofloxacin. Mylan also claims that Daiichi failed to submit oral toxicity studies that concluded that levofloxacin was not less toxic than ofloxacin.

In the '407 patent application, Daiichi provided comparative toxicity data for ofloxacin, levofloxacin, and the dextrorotatory enantiomer of ofloxacin. (DX 8 at 29.) The data in the patent application reads as follows:

Acute Toxicity

The acute intravenous toxicity of (±), R(+) and S(-) forms of Ofloxacin in male mice is shown in Table 3 below.

Table 3

Compounds	Dose (mg/kg)	Numbers of Mice	Day after Treatment			Mortality
			1	2	3	
(±)	100	5	0	0	0	0/5
	200	5	2	0	0	2/5
	500	5	5	0	0	5/5
R(+)	100	5	0	0	0	0/5
	200	5	3	0	0	3/5
	500	5	5	0	0	5/5
S(-)	100	5	0	0	0	0/5
	200	5	0	0	0	0/5
	500	5	5	0	0	5/5

LD_{50} (i.v. in mice)
(±)-form 203 mg/kg
S(-)-form 244 mg/kg

(DX 8 at 29.) Daiichi underscored the significance and the surprising nature of levofloxacin's low toxicity in its requests for reconsideration. (DX 8 at 81-83, 205.) The table, which eventually became Table 3 of the '407 Patent (DX 1), reveals that fewer mice died at the 200 mg/kg dose of levofloxacin (zero out of five mice) than died at the same dose of the dextrorotatory enantiomer (three out of five mice) and ofloxacin (two out of five mice). Based on this data alone, Daiichi toxicologist Dr. Furuhama determined that levofloxacin was less toxic than ofloxacin and reported this conclusion to Dr. Hayakawa. (Furuhama Tr. at 4578-80.)

Below the table, the patent application reported LD_{50} values for levofloxacin (244 mg/kg) and ofloxacin (203 mg/kg).[14] (DX 8 at 29.) An "LD_{50}" is a measure of toxicity representing the dose at which fifty percent (50%) of the animals to which a drug is administered die. Thus, a higher LD_{50} indicates a lower toxicity. (Mitscher Tr. at 687.) Moreover, an LD_{50} value can be verified only after one proves that the data would follow a "normal distribution." (Furuhama Tr. at 4581-82.)

The reported LD_{50} value is the "value which would lie right at the center of the values which fall within the 95 percent

[14] The 203 value was a typographical error. The LD_{50} value should have been 208.

confidence limit." (Id. at 4582.) The confidence limits or intervals for levofloxacin and ofloxacin express the range of confidence in a given LD_{50} value, like a margin of error. The internal handwritten memorandum dated January 23, 1986, in which Dr. Furuhama first reported the LD_{50} values, did not contain confidence intervals. (PX 3144; Furuhama Tr. at 4590.) The LD_{50} confidence intervals for levofloxacin and ofloxacin were, however, later calculated at Daiichi during the prosecution of the '407 patent. (Hayakawa Tr. at 4339-40, 4408) The LD_{50} for levofloxacin was calculated at 243.8 mg/kg with a confidence range from 211.4 - 274.0 mg/kg compared to ofloxacin's 208 mg/kg with a confidence range of 194-223 mg/kg. (DX 302; DX 303.)

In addition to the acute i.v. toxicity tests on mice, there were numerous oral toxicity tests performed by Daiichi during the prosecution of the '407 patent, some of which described ofloxacin as either equally toxic or less toxic than levofloxacin. (DX 179/T; DX 300/T; DX 234/T; DX 266/T.) Those studies were submitted to the FDA but not to the PTO. (DX 44; DX 39.)

Despite Mylan's contentions, neither the lack of confidence intervals nor the failure to submit oral toxicity data was a material omission. "[I]n small studies of acute toxicity leading to death," confidence intervals are "not very important." (Rodricks Tr. at 4633.) Because of the breadth of the confidence

intervals in studies with few data points, it is not unusual for two compounds with very different lethalities to have overlapping confidence intervals at the margins. (Id.) Furthermore, with respect to the specific confidence intervals at issue in the case at bar, the overlap in the confidence intervals of levofloxacin and ofloxacin is so slight that they suggest only a two percent chance that levofloxacin is not less toxic than ofloxacin. (Id. at 4706-07.) Finally, in such small studies, it is "very common" for LD_{50} values to be reported without confidence limits. (Id. at 4703.) Thus, although the LD_{50} values and confidence limits are intrinsically "linked" statistically, the confidence limits were sometimes omitted from internal Daiichi comparisons of the LD_{50} values of levofloxacin and ofloxacin. (DX 244T; PX 3144.)

Ortho also offered significant evidence that the oral toxicity tests were poor measures of inherent toxicity. According to the testimony offered by Daiichi toxicologist, Dr. Furuhama, and Daiichi's expert on toxicology, Dr. Rodricks, the sole testimony the Court received from toxicologists, acute oral toxicity tests are not helpful in precisely determining toxicity because oral administration creates too many other variables. Dr. Furuhama identified these variables, such as solubility and absorption rate, as "confounding factors . . . [that] would affect the toxicity level obtained." (Furuhama Tr. at 4578.) He further noted that a

test of intrinsic toxicity, like the acute i.v. test, was superior because it "would be devoid of those confounding factors." (Id.) This opinion was echoed by Dr. Rodricks, who stated that acute oral toxicity tests were not "reliable indicators of inherent" toxicity because "at the doses used in the studies, they do not distinguish toxicity from other factors that influence the absorption of the compound into the blood." (Rodricks Tr. at 4635.)

Mylan provided only weak evidence that oral toxicity tests were material. Although Dr. Siporin, an expert in drug development, opined that oral toxicity tests are relevant because levofloxacin is administered orally, (Siporin Tr. at 2548), he admitted that he is neither a toxicologist nor an expert in toxicology. (Id. at 2421.) Furthermore, one of Mylan's other experts, Dr. Mitscher, admitted that when the solubilities of two compounds are different, it is difficult to compare their toxicity through oral toxicity experiments. (Mitscher Tr. at 1145-46.)

To compensate for its lack of qualified expert rebuttal testimony on the toxicity issue, Mylan argues that all toxicity studies submitted to the FDA, including the oral toxicity studies, should have been submitted to the PTO. Nonetheless, Daiichi's submission to the FDA only demonstrates that the tests were performed and available for submission. The mere existence of these tests does not establish why a reasonable administrator would

be interested in reviewing them. Without a threshold showing of relevance to the Examiner's ultimate determination of the comparative toxicities of levofloxacin and ofloxacin, the fact that the oral toxicity tests were among the massive volume of materials submitted to the FDA is of no moment.[15]

Additionally, there is no evidence of intent to mislead the Examiner as to the relative toxicities of levofloxacin and ofloxacin because Daiichi had reliable evidence that levofloxacin was less toxic. Before the Daiichi applicants filed their July 1988 Request for Reconsideration, the results of a GLP[16] toxicity test were reported internally, in which the LD_{50} value of levofloxacin was shown to be 268 mg/kg, as opposed to 208 mg/kg for ofloxacin, with no overlap of confidence intervals. (PX 369/T; PX 1/T; PX 3185; Rodricks Tr. at 4631-4633, 4715.)

Accordingly, Mylan has failed to prove materiality or intent by clear and convincing evidence. It has failed to prove the

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[15] Notwithstanding Mylan's suggestion to the contrary, the Court cannot infer intent from the mere failure to submit material to the PTO that was later submitted to the FDA, because there are different standards for disclosure. The case on which Mylan relies for this argument, Danbury Pharmacutical, 873 F.2d at 1419-20, does not create a blanket rule but rather involved an inference of intent when the patentee failed to disclose multiple prior art references to the PTO that were submitted to the FDA. Danbury Pharmacutical was a specialized case that involved a high level of materiality supporting an inference of intent.

[16] GLP denotes "good laboratory practices" studies, which are performed for regulatory submissions.

materiality of the missing confidence intervals or the undisclosed oral toxicity tests. It has provided no direct evidence of intent; nor has it proven a representation or omission sufficiently material to imply an intent to mislead. Accordingly, the Court cannot find that Daiichi acted inequitably with respect to its toxicity claims.

b. Solubility

Mylan also alleges that Daiichi acted inequitably by (1) omitting data indicating that the solubility of levofloxacin was not ten times higher than ofloxacin at all pH levels, (2) making a misleading statement that the increased solubility was surprising, and (3) making a misleading statement that ofloxacin was unsatisfactory for aqueous preparations. Mylan has failed to demonstrate by clear and convincing evidence that either the alleged omission was material or that the alleged representations were materially false or misleading.

Daiichi submitted solubility data to the PTO in Table 4 of the '407 patent application. (DX 8 at 30.) The data indicates that the solubility of the enantiomers and the racemate in water at a temperature in the range of 23° to 26° C were measured as: ofloxacin: 2,400 µg/ml, the dextrorotatory enantiomer: 25,800 µg/ml, and levofloxacin: 22,500 µg/ml.

In a January 20, 1988 Office Action, the PTO rejected the claims of the application as obvious, finding the invention "unpatentable over Hayakawa et al. [U.S. Patent 4,382,892 (ofloxacin)], the Japanese patent or the acknowledged prior art on page 1 of the specification." (DX 8 at 69.) The Examiner stated: "The present compounds are the specific optical isomers of known compounds. To resolve and identify the more active isomer is held to be within the skill of the worker in the art." (Id.)

In response to the Examiner's initial rejection, Daiichi, through its attorney, stated that it was "unexpected" that levofloxacin "has a water solubility of about 10 times higher than that of the racemic compound . . . in water in a neutral pH range . . . ." (DX 8 at 82.) Further, it stated that the increased solubility "makes it possible to administer the claimed compounds parenterally in an aqueous preparation, whereby the compounds can be administered in various dosage forms. Of course, Ofloxacin per se has a relatively high water-solubility as compared with other synthetic antibiotics, but the water solubility of Ofloxacin is still considered unsatisfactory for use as aqueous preparations." (Id.) After the Examiner's second rejection, Daiichi submitted a second request for reconsideration containing identical language regarding levofloxacin's solubility. (DX 8 at 206.)

Mylan argues that the statements were misleading and inaccurate because Daiichi chose neutral pH as the sole reference point, rather than reporting solubility across a range of pH values. Daiichi's statement to the PTO that levofloxacin is ten times more soluble than ofloxacin at a neutral pH in water, however, was not false or misleading.

Although Daiichi only reported the relative solubility at one pH, it clearly stated (in its requests for reconsideration) that the measurement was taken at a neutral pH, which negated anything misleading about the statement. (DX 8 at 82, 206.) Further, Daiichi knew that the relative solubility of levofloxacin and ofloxacin varied with pH (Hayakawa Tr. at 4274), and it measured its solubility using the methods prescribed by Japan's pharmacopoeia (standards governing medicinal drugs), (PX 3203; Hayakawa Tr. at 3957-61), rebutting any suggestion that its measurement was biased.

Nonetheless, Mylan has identified one definite inaccuracy: Daiichi's statement that it measured the solubility "in water." (Hayakawa Tr. at 4273.) That statement was technically incomplete because the water used by Daiichi had sodium hydroxide in it. (Id.) This inaccuracy, however, does not weigh in favor of a finding of inequitable conduct because it is immaterial. The

addition of sodium hydroxide is "irrelevant" to the water solubility determination. (Id.) Mylan fails to show otherwise.

There is no evidence of an intent to deceive the PTO as to the relative solubilities of levofloxacin and ofloxacin. Contemporaneous internal Daiichi documents indicate that, based on experimental data, Drs. Hayakawa and Atarashi found that the solubility of levofloxacin was 22,500 µg/ml, approximately ten times the solubility of ofloxacin, a finding they contemporaneously described as "an extraordinary value." (PX 872; PX 161; Hayakawa Tr. at 3952-53, 3969-72). That was the same figure reported in the '407 patent application. (DX 8 at 404.) The Daiichi scientists were especially impressed with levofloxacin's solubility because they had believed that the enantiomers of ofloxacin would have a lower solubility than their racemate. (Hayakawa Tr. at 3970.) In light of the contemporaneous recordings and the credible testimony of Dr. Hayakawa on this issue, Mylan cannot meet its burden of demonstrating that Daiichi intended to mislead the PTO, either in its statements that levofloxacin was ten times more soluble than ofloxacin or in its statement that the increase in solubility was surprising.[17]

[17] Moreover, Dr. Myerson, the sole solubility expert at trial, testified that the relative water solubility of levofloxacin is approximately ten times that of ofloxacin. (Myerson Tr. at 4106.)

Mylan also argues that Daiichi's statements to the PTO regarding the relative utility of levofloxacin and ofloxacin for use in aqueous preparations were misleading because they allegedly suggested that ofloxacin could not be used for aqueous preparations when in fact it is undisputed that ofloxacin is used for aqueous preparations. This contention focuses on the language in the requests for reconsideration, in which Daiichi stated that "Ofloxacin is still considered unsatisfactory for use as aqueous preparations." (DX 8 at 82, 206.)

Daiichi concedes that its word choice was poor. Nevertheless, it maintains that the statement can logically be understood to mean that ofloxacin is relatively less satisfactory than levofloxacin, but not necessarily useless, for aqueous preparations. It argues that such a construction is reasonable because the statement was coupled with a laudatory statement about ofloxacin's solubility and because the examiner reviewing the '407 patent had been the examiner for ofloxacin and would have known it was not useless for aqueous preparations. The plaintiffs also highlight Dr. Hayakawa's poor command of the English language as a factor in the poor word choice.

Addressing the translation issue first, the Court cannot absolve foreign patentees of their duty to accurately prosecute their patent applications because of their lack of facility with

the English language. That would set a dangerous precedent. Nevertheless, the word "unsatisfactory," can be read as "insufficient" or "inadequate," The Oxford Reference Dictionary 735 (1st ed. 1986), rather than the meaning that Mylan would ascribe to it - useless. Moreover, the statement that ofloxacin is "unsatisfactory" was made in the context of discussing that compound's high solubility, which weighs against an interpretation that Daiichi was characterizing ofloxacin as totally unusable for aqueous preparations. As Mylan's expert, Professor Mitscher, observed, "it is not a very clear sentence." Under the clear and convincing evidence standard applicable to the intent inquiry, however, lack of clarity and poor draftsmanship by attorneys cannot serve as a basis for either finding that a statement was false or inferring intent to deceive.

The Court's finding that the statement could not have been materially misleading is further reinforced by the fact that, as already noted, the same examiner reviewed both the levofloxacin and the ofloxacin patents. As Mitscher admitted, the ofloxacin patent was also before the Examiner as prior art and that patent application stated that ofloxacin is injectable. (Mitscher Tr. at 1133-34.)

Finally, the evidence at trial demonstrated that levofloxacin does have advantages over ofloxacin for use in aqueous

preparations. Dr. Hayakawa testified that ofloxacin's limitations included the need to adjust its pH value (Hayakawa Tr. at 4235-36.), the possible development of crystal urea, (id. at 4000-01), and licensee dissatisfaction with ofloxacin eyedrops. (Id. at 4004-05, 4236.) This final limitation was further explained by another of plaintiffs' experts, Dr. Hwang, who testified that levofloxacin's greater solubility makes it a superior drug for combating certain eye infections. (Hwang Tr. at 3453.) Dr. Hwang explained that the higher solubility of levofloxacin allows it to be formulated at a higher concentration than ofloxacin for ophthalmic use, thus achieving a higher effective concentration in the tissues when applied to the eye. (Id. at 3430-31.) Even Dr. Mitscher admitted that levofloxacin was more soluble than ofloxacin, and that the difference was clinically significant. (Mitscher Tr. at 1126-27.)

Mylan has failed to prove materiality or intent by clear and convincing evidence. Although it may have proven that Daiichi is guilty of poor word choice, it has failed to prove that any of its statements were materially misleading. It has provided no direct evidence of intent, nor has it proven a representation or omission sufficiently material that the Court could infer intent to mislead. Accordingly, the Court cannot find that Daiichi acted inequitably with respect to its solubility claims.

c. Failure to Disclose the 1985 Gerster Reference

Mylan contends that Daiichi committed another material omission by failing to submit a 1985 reference to work performed by Dr. John F. Gerster involving the separation of another racemic fluoroquinolone, flumequine, into its enantiomers. Specifically, it argues that Gerster's work taught that the levorotatory enantiomer would likely be more potent than the racemate.

During prosecution of the '407 patent, Daiichi submitted two references to Gerster's work on flumequine. It provided the first of these references on July 8, 1988, the same day as its first request for reconsideration. (DX 8 at 141-91.) The reference was a 1987 article by J. F. Gerster, et al. (the "1987 Gerster"). (Id. at 187-91). The Examiner subsequently used this reference as an additional reason for finding levofloxacin obvious in its September 2, 1988 rejection. (Id. at 193) (finding the patent obvious over the ofloxacin patent "in view of the [1987] Gerster et al. article newly cited by applicants."). The Examiner had found the article significant because, in the article, the "optical isomers of flumequine (a related tricyclo quinolizine carboxylic acid of the same use) show 'markedly different antibact[e]rial potency.'" (Id. at 193.)

In response to this rejection, Daiichi asserted that the reference "cannot aid the rejection based on Hayakawa et al. since

its publication date is after the filing date of the present application. Note that the article was not even received until September 5, 1986." (Id. at 207.) On March 8, 1989, Daiichi submitted another reference to Gerster's work with flumequine, a one page summary describing that he had successfully separated the flumequine enantiomers and explaining that a presentation was to be given on the "synthesis and antibacterial activity of flumequine, its optical isomers and desmethyl analog . . . ." (Id. at 209-10, 268.) That reference was dated 1982 (the "1982 Gerster Abstract").

Despite these disclosures, Mylan maintains that Daiichi was also under a duty to disclose a reference that Dr. Hayakawa received at a conference held in Minneapolis from September 29-October 2, 1985 (the "1985 Gerster"). (Gould Tr. at 233; DX 35.) Dr. Hayakawa admitted receiving the reference and using it in creating Process C, an efficient method of synthesizing levofloxacin. (Hayakawa Tr. at 3211-12.) He further testified that, although it was never submitted to the PTO, he had submitted the 1985 Gerster to Daiichi's patent counsel, Mr. Sakamoto, for that purpose. (Id.)

Daiichi's failure to disclose the 1985 Gerster was not material. First, the publication of that reference succeeded the June 20, 1985 priority date; therefore, it is not prior art. Secondly, the reference was constructively disclosed because it was

described in footnote 6 of the 1987 Gerster, which Daiichi had submitted to the Examiner. (DX 8 at 188.) Finally, the information in the 1985 Gerster is largely cumulative of the 1987 Gerster, containing the same language on which the Examiner relied as a secondary basis for finding the '407 patent obvious. (Gould Tr. at 249-50; DX 8 at 193; DX 35.) Indeed, "a patentee need not cite an otherwise material reference to the PTO if that reference is merely cumulative or is less material than other references already before the examiner." Baxter Int'l, Inc. v. McGaw, Inc., 149 F.3d 1321, 1328 (Fed. Cir. 1998) (citations omitted).

Furthermore, Dr. Hayakawa's unrefuted testimony that he intended the disclosure of the 1985 Gerster, combined with the disclosure of the 1987 Gerster, indicates that Daiichi acted in good faith. The 1985 Gerster would prompt the same obviousness arguments as the 1987 Gerster, and neither of the references constitutes prior art. Thus, Daiichi simply had no reason to hide one reference while disclosing the other. Moreover, Daiichi's voluntary, though unnecessary, disclosure of the 1987 Gerster harmed its chances of patenting levofloxacin. Therefore, Mylan has failed to adduce evidence of intent to deceive the PTO by the withholding of the 1985 Gerster.

In conclusion, the evidence establishes that disclosure of the 1985 Gerster abstract would have been unnecessary and ineffectual.

Therefore, Mylan is unable to demonstrate, by clear and convincing evidence, that Daiichi's failure to disclose that abstract was a material omission or intentionally deceptive.

d. Representations Regarding the 3-Methyl Group

Finally, Mylan asserts that Daiichi's statements regarding the 3-Methyl Group[18] were untrue, material and misleading. Specifically, in support of its argument that levofloxacin's superior potency relative to ofloxacin was surprising, Daiichi stated:

> The reason [for its surprise] therefore is that the excellent activity of Ofloxacin had been considered to be attributable to a combination of a unique main structure, which had not been found in the conventional antibiotics, and the substituents attached to the 9- and 10-positions, especially in view of the fact that a compound having the same structure as Ofloxacin but having no methyl group at the 3-position also exhibits an excellent antimicrobial activity, though its activity is somewhat weaker than that of Ofloxacin. Thus, applicants as those of skill in the art considered that the steric configuration of the 3-methyl group does not or substantially does not affect the antimicrobial activity of Ofloxacin.

(DX 8 at 79-80.)

Mylan argues that Daiichi was being deceptive by classifying desmethyl ofloxacin as only "somewhat weaker" than ofloxacin, (DX 8 at 80), while categorizing the difference in antimicrobial activity between levofloxacin and ofloxacin as "significant." (DX

[18] In ofloxacin, the "3-Methyl Group" is a methyl group, i.e., CH_3, at the 3-position in the molecular structure.

8 at 205.) Dr. Hayakawa admitted that the difference between the activity of desmethyl ofloxacin versus ofloxacin and ofloxacin versus levofloxacin is either the same or the former difference is greater. (Hayakawa Tr. at 4213) (stating that "the antimicrobial activity of the desmethyl as compared to ofloxacin was about a half to a quarter . . . ."). Therefore, Mylan argues that the suggestion that the desmethyl ofloxacin was only "somewhat weaker" than ofloxacin was a gross understatement.

These comparative statements, however, are not the earthquakes that Mylan suggests. The terms "somewhat weaker" and "significant" are not polar opposites. Rather, as Daiichi's expert, Dr. Wentland, explained, one comparison was between an enantiomer and its racemate, where a two-fold difference in activity is the maximum possible difference and is, therefore, "significant." (Wentland Tr. at 4529.) A much greater variance is possible between two distinct chemical structures, such as ofloxacin and the desmethyl compound, where a variation in structure can cause a decrease in antimicrobial activity of as much as 10,000 fold. (Id. at 4528.)

Viewed in those terms, the Court cannot conclude that it was misleading for Daiichi to refer to the maximum possible difference as "significant," and a relatively small difference compared to the maximum possible difference as "slight." This is consistent with

the understanding of Dr. Hayakawa, who testified that what constitutes a substantial difference in activity depends on the compounds being compared. (Hayakawa Tr. at 4341-44.) Specifically, he testified that, in comparing the activity of ofloxacin and desmethyl ofloxacin, "a difference in antimicrobial activity of two, a two-fold difference ordinarily would not be considered to be a substantial difference." (Id. at 4344.)

Mylan alleges that the 1982 Gerster Abstract demonstrates that Hayakawa deliberately misled the PTO as to the significance of the 3-Methyl Group because it discloses that the same phenomenon was observed in flumequine, the only other chiral fluoroquinolone of note at the time. There, Gerster teaches that one of the flumequine enantiomers exhibits significant potency while the other does not, and that the desmethyl analog of flumequine showed less activity than flumequine itself. (DX 34; DX 8 at 268.)

The 1982 Gerster Abstract does not, however, support a finding of intentional deception by Daiichi. There are profound differences between flumequine and ofloxacin that would discourage a skilled artisan during the relevant period from concluding that one of the ofloxacin enantiomers would exhibit higher antimicrobial activity than the other enantiomer or racemic ofloxacin. (Klibanov Tr. at 2055-62; Wentland Tr. at 4513-17) Dr. Klibanov, for example, opined that it would be "scientifically improper" to

extrapolate from the experience with a single compound. (Klibanov Tr. at 2061-62.) Moreover, to the extent that the 1982 Gerster Abstract taught a conclusion inconsistent with that of Dr. Hayakawa, that abstract was disclosed.

That Daiichi was not attempting to mislead the Examiner with its characterization of the predictive value of the desmethyl analog is strongly supported by the data provided in a 1984 article authored by Dr. Hayakawa. (DX 8 at 141, 180-91.) The article was submitted to the Examiner on July 8, 1988, and was one of the key prior art references considered. As Dr. Mitscher admitted, not only was the article submitted to the Examiner, its relevant data was separately summarized during the course of the prosecution history. (Mitscher Tr. at 1076.) This data included the exact MIC values for levofloxacin, ofloxacin, and desmethyl ofloxacin, among other compounds. Thus, the Examiner was notified of the compounds' comparative potencies.

Mitscher could offer only one explanation as to why the generalized comparative statements would be considered, while the data was ignored: the Examiner may not have had the time to determine the validity of the attorney arguments. Such speculation about which statements in the prosecution history were read by the examiner is unhelpful, however; guessing cannot support Mylan's burden of proving materiality or intent by clear and convincing evidence. Accordingly, there is insufficient evidence from which

to conclude that Daiichi acted inequitably with respect to its representations about the 3-Methyl Group.

e. Conclusion on Inequitable Conduct

Mylan's evidence fails clearly and convincingly to establish that Daiichi committed intentionally deceptive acts or omissions regarding material information during the prosecution of the '407 patent. Therefore, the patent is not invalid for inequitable conduct.

B. Obviousness

1. Standard of Law

A patent claim is invalid "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). The obviousness inquiry is a question of law that requires specific factual findings, which include "the scope and content of the prior art, the level of ordinary skill in the field of the invention, the differences between the claimed invention and the prior art, and any objective evidence of non-obviousness . . . ." SIBIA Neurosciences v. Cadus Pharm. Corp., 225 F.3d 1349, 1355 (Fed. Cir. 2000) (citing Graham v. John Deere Co., 383 U.S. 1, 17-18 (1966)). The Court presumes an issued patent's validity; therefore, the defendant bears the burden of proving each fact underlying an obviousness determination

by clear and convincing evidence. Id. (citation omitted); Beckson Marine, Inc. v. NFM, Inc., 292 F.3d 718, 725 (Fed. Cir. 2002).

When the disputed claim is a chemical compound, "a prima facie case of obviousness requires 'structural similarity between claimed and prior art subject matter . . . where the prior art gives reason or motivation to make the claimed compositions." Yamanouchi Pharm. Co., Ltd. v. Danbury Pharmacal, Inc., 231 F.3d 1339, 1343 (Fed. Cir. 2000) (quoting In re Dillon, 919 F.2d 688, 692, (Fed. Cir. 1990) (en banc)).[19] The prior art also must offer a "reasonable expectation of success," though "not absolute predictability," in guiding a skilled artisan toward production of the claimed compound at the time of the invention. Id. at 1343, 1345 (quoting In re Longi 759 F.2d 997, 896 (Fed. Cir. 1985)). As § 103(a) instructs, however, the obviousness analysis must consider the claimed chemical compound "as a whole." See Dillon, 919 F.2d at 697 ("[A]

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[19] Mylan asserts that enantiomers are prima facie obvious vis-a-vis the racemic compound. See In re Jones, 958 F.2d 347, 350 (Fed. Cir. 1992) (citing In re May, 574 F.2d 1082 (C.C.P.A. 1978)). Although Jones and May support Mylan's contention, they are inconsistent with the Federal Circuit's directive to make Graham findings in every case to establish a prima facie case of obviousness. See, e.g., In re Mayne, 104 F.3d 1339, 1341 (Fed. Cir. 1997) (applying the Dillon structural similarity framework to an isomer compound); Ruiz v. A.B. Chance Co., 234 F.3d 654, 663 (Fed. Cir. 2000).

Similarly, the principle that "each obviousness determination rests on its own facts" militates against any narrowly applied rule of prima facie obviousness. Mayne, 104 F.3d at 1341; see also In re Grabiak, 769 F.2d 729, 731 (Fed. Cir. 1985) ("[G]eneralization should be avoided insofar as specific chemical structures are alleged to be prima facie obvious one from the other."). Irrespective of Mylan's prima facie burden, however, the Court reaches the same ultimate conclusion as to the non-obviousness of the '407 patent.

compound and all of its properties are inseparable.") Therefore, in the case at bar, Mylan must prove that, as of June 20, 1985, the prior art would not only motivate a person of ordinary skill in the art to make levofloxacin but also reasonably suggest that the compound would exhibit its unique combination of properties. Yamanouchi Pharm., 231 F.3d at 1345.

If Mylan meets its initial burden, Daiichi/Ortho can rebut the prima facie case of obviousness by offering evidence of "'unexpected results,' i.e., [showing] that the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected." In re Soni, 54 F.3d 746, 750 (Fed. Cir. 1995). Such unexpected results must be established by objective, factual evidence--not mere argument or conclusory statements. Id. Moreover, since structurally similar compounds generally have similar properties, an unexpected result must be a substantial improvement over the prior art. In re Geisler, 116 F.3d 1465, 1471 (Fed. Cir. 1997) (citing Soni, 54 F.3d at 751). The patentee can also rebut a prima facie case by proffering evidence of secondary considerations, which alone may defeat a claim of obviousness. See, e.g., In re Beattie, 974 F.2d 1309, 1313 (Fed. Cir. 1992).

2. Findings of Fact and Conclusions of Law

a. Graham Factors

The Federal Circuit unambiguously directs courts to make "Graham findings" in evaluating whether a patent is obvious. Ruiz v. A.B. Chance Co., 234 F.3d 654, 663 (Fed. Cir. 2000); see also Yamanouchi Pharm., 231 F.3d at 1343. Under the first three so-called "Graham factors," the Court must determine the scope and content of the prior art, the level of skill in the relevant art, and the differences between levofloxacin and the prior art. These inquiries underpin--and thus necessarily precede--the Court's analysis of Mylan's prima facie case based on structural similarity.

i. Scope and Content of the Prior Art

"The scope of the prior art includes art that is 'reasonably pertinent to the particular problem with which the invention was involved.'" Ruiz, 234 F.3d at 666-67 (quoting Stratoflex, Inc. v. Aeroquip Corp., 713 F.2d 1530, 1535 (Fed. Cir. 1983)).

> The prior art primarily comprises references that are within the field of the inventor's endeavor. References that are not within the field of the inventor's endeavor may also be relied on in patentability determinations, and thus are described as "analogous art," when a person of ordinary skill would reasonably have consulted those references and applied their teachings in seeking a solution to the problem that the inventor was attempting to solve.

Heidelberger Druckmaschinen AG v. Hantscho Commercial Prods., 21 F.3d 1068, 1071 (Fed. Cir. 1994). Prior art also necessarily includes references that "might lead away from the claimed invention." In re Dow Chem. Co., 837 F.2d 469, 473 (Fed. Cir. 1988). In any event, a prior art reference must be available before the date of invention--June 20, 1985. Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc., 796 F.2d 443, 449 (Fed. Cir. 1986).

The parties do not dispute that the closest prior art to levofloxacin is ofloxacin, i.e., the '892 patent. In addition, the Court finds that relevant prior art references include literature in the field of stereochemistry, particularly that which pertains to the unique characteristics of enantiomers, ofloxacin and quinolones.

ii. Level of Ordinary Skill in the Art

Whether the claimed invention is obvious must be evaluated from the perspective of a hypothetical person of ordinary skill in the art. Standard Oil Co. v. Am. Cyanamid Co., 774 F.2d 448, 454 (Fed. Cir. 1985). This hypothetical person presumptively "thinks along the line of conventional wisdom in the art and is not one who undertakes to innovate, whether by patient, and often expensive, systematic research or by extraordinary insights." Id. To determine the ordinary level of skill in the art, the Court must consider the following factors: "1) the types of problems

encountered in the art; 2) the prior art solutions to those problems; 3) the rapidity with which innovations are made; 4) the sophistication of the technology; and 5) the educational level of active workers in the field." Ruiz, 234 F.3d at 666-67 (citation omitted). "Not all such factors may be present in every case, and one or more of them may predominate." Id. (quotation omitted).

The parties offer similar definitions of the level of ordinary skill in the art. As such, the Court finds that a person of ordinary skill in the art would have had an advanced degree (though not necessarily a doctorate) in chemistry or a related discipline, which included the study of stereochemistry. A skilled artisan also would have had either (a) substantial laboratory or clinical experience in pharmaceutical research and development or (b) substantial familiarity with principles of pharmacology and pharmaceutical synthesis. (Klibanov Tr. 1877-79; Mitscher Tr. 523-28.)

iii. Differences Between Levofloxacin and the Prior Art

As noted, it is undisputed that ofloxacin is the closest prior art to the levofloxacin claimed in the '407 patent. Accordingly, the differences between ofloxacin and levofloxacin are of primary importance in the obviousness analysis. On a molecular level, levofloxacin is one of two optical isomers comprising the racemic

compound of ofloxacin. Thus, the two compounds share the same chemical composition but differ in the spatial arrangement of their atoms. (Mitscher Tr. at 1169.) With respect to the compounds' respective properties, the parties focus on quantitative differences in antimicrobial activity, solubility and toxicity.

As an initial matter, the parties agree that levofloxacin is twice as active as ofloxacin. No such consensus exists, however, as to the relative differences in solubility between levofloxacin and ofloxacin. The issue of solubility turns on the appropriate conditions of measurement. Mylan contends that the solubility of levofloxacin should be measured at equilibrium in water. Under those conditions, levofloxacin appears to be five times more soluble than ofloxacin. (PX 137 at DAI-0021137.) However, according to Dr. Allan Myerson, the only solubility expert to testify at trial, solubility calculations of the hemihydrate form of levofloxacin (the only form used on the market) properly use non-equilibrium measurements. (Id. at 4156-57.) Dr. Myerson also opined that levofloxacin is approximately ten times more soluble than ofloxacin at neutral pH. (Myerson Tr. at 4106.) Mylan did not proffer any evidence directly rebutting Dr. Myerson's methodology as to non-equilibrium solubility measurements of hemihydrates and

other metastable phases.[20] Therefore, without any compelling reason to doubt the scientific basis of his expert opinion, the Court finds that Dr. Myerson's testimony is credible and consistent with Daiichi's initial conclusions about the solubility of levofloxacin. (PX 872; PX 161.) Accordingly, the Court finds that the relative solubility of levofloxacin is approximately ten times greater than the relative solubility of ofloxacin at neutral pH.

The parties also disagree about the relative toxicities of levofloxacin and ofloxacin. Daiichi/Ortho maintains that levofloxacin is less toxic than ofloxacin. Relying heavily on oral toxicity tests and numerous statements by the plaintiffs, Mylan argues that any difference in the two compounds' toxicity is neither statistically significant nor toxicologically meaningful.

As discussed under the issue of inequitable conduct, however, Mylan's argument that oral toxicity tests produce reliable toxicity data is unpersuasive. (See Rodricks Tr. at 4635.) Moreover, Dr. Rodricks, the sole toxicologist to testify at trial, opined that, in both human studies and pre-clinical animal testing, levofloxacin has "consistently" shown "reduced toxicity relative to ofloxacin." (Id. at 4768.) Ample data support this opinion, including i.v.

[20] The Court also notes that, in discussing his optical purity calculations, Dr. Mitscher emphasized the distinction between the hemihydrate form and the other forms of levofloxacin. (Mitscher Tr. at 754, 900-01.)

studies in mice and rats, CNS studies, and adverse event reports. (See PX 3199, PX 3186, PX 369/T at DAI-0120628, PX 1/T, PX 10/T at DAI-0011720, PX 255/T at DAI-0054119, PX 375/T, PX 260/T, PX 2951A at 9, PX 2750 at ORTHO 0511139, PX 2759 at ORTHO 0511188.) Taken as a whole, this evidence provides a reasonably accurate indicator of clinical safety and relative toxicity. (See, e.g., Hooper Tr. at 1541-45.) Therefore, the Court finds that levofloxacin is appreciably less toxic than ofloxacin.

b. Mylan's Prima Facie Case of Structural Obviousness

Daiichi/Ortho concedes that levofloxacin is structurally similar to its racemate, ofloxacin. (Pl. Post-Tr. Br. at 13.) Thus, Mylan has the burden to prove by clear and convincing evidence that the prior art motivated a person of ordinary skill in the art to produce levofloxacin with a reasonable expectation of success. The standard here is not whether generating levofloxacin was "obvious to try." In re Eli Lilly and Co., 902 F.2d 943, 945 (Fed. Cir. 1990).

> An 'obvious-to-try' situation exists when a general disclosure may pique the scientist's curiosity, such that further investigation might be done as a result of the disclosure, but the disclosure itself does not contain a sufficient teaching of how to obtain the desired result, or that the claimed result would be obtained if certain directions were pursued.

Id. (citing In re O'Farrell, 853 F.2d 894, 903-04 (Fed. Cir. 1988)). Therefore, the patent challenger must show the following:

(1) a "clear and particular" suggestion or reason to combine relevant prior art references; (2) sufficient guidance within the combined references to obtain the patented invention with a reasonable expectation of success; and (3) sufficient teaching in the prior art to indicate that the end product is reasonably likely to exhibit the patented invention's unique combination of properties. Id.; Ruiz, 234 F.3d at 665; Yamanouchi Pharm., 231 F.3d at 1343, 1345. "Reasonable expectation of success is assessed from the perspective of the person of ordinary skill in the art." Life Techs., Inc v. Clontech Labs., Inc., 224 F.3d 1320, 1326 (Fed. Cir. 2000).

i. Motivation to Combine

Mylan offers persuasive evidence demonstrating the requisite level of motivation in the prior art. In this regard, the 1982 Gerster Abstract is particularly significant. (DX 34.) That abstract reported the separation of the enantiomers of flumequine, specifically indicating that the S(-) isomer had more "potent antibacterial activity" compared to the "very weak activity" of the R(+) isomer. (Id.; Klibanov Tr. at 2054-55.) It is undisputed that, as of mid-1985, "ofloxacin and flumequine were the only two reported fluoroquinolone antibacterial[s] of any note that had a chiral center." (Tr. 3625.)

Although ofloxacin and flumequine molecules possess fundamentally different structures, the Gerster abstract did not attribute the differences of activity in the flumequine enantiomers to structure. As such, this reference provided the raw motivation to a person of ordinary skill in the art to apply known methods of enantiomeric separation to ofloxacin. Dr. Hayakawa's subsequent statements in a book chapter confirm the presence of ample motivation to separate the optical isomers of ofloxacin. (PX 382/T.) He wrote:

> [W]ith the development of synthesis methods via stereoselection and improvement in the analytical methods of optical isomers in the recent years, many came to believe that only one of the enantiomers is the important substance and that the other one is, if bluntly said, almost an impure substance. Influenced by ideas like these, we decided to focus on the antibacterial activity of the two [ofloxacin] enantiomers, resulting in the application of optical resolution.[21]

(Id.)

ii. Guidance in the Prior Art to Produce the Invention

Whether a skilled artisan would have a reasonable expectation of success in obtaining levofloxacin presents a more difficult question. Various methods of separating enantiomers were well

[21] This is an important admission rebutting Daiichi/Ortho's assertion that structure-activity relationship principles would have completely discouraged skilled artisans from either attempting to separate ofloxacin's enantiomers or reasonably expecting that one enantiomer would exhibit greater activity than the racemate.

known by persons of ordinary skill in the art in June, 1985. The synthesis of pure optical isomers from racemic compounds, however, was tedious and uncommon at the time. (PX 795 at col 2, lines 62-65; Klibanov Tr. at 2070-71; Myerson Tr. at 4193.) According to Daiichi/Ortho, obtaining the isomers of ofloxacin proved especially difficult. Daiichi first endeavored to synthesize the enantiomers of ofloxacin in early 1981, but as of March, 1984, every conventional attempt to do so had failed. (Hayakawa Tr 4032-33; id. at 4053.) The Daiichi researchers subsequently developed three "novel" processes to separate the ofloxacin enantiomers. (See Mitscher Tr. at 1016-18, 1023-24; Klibanov Tr. at 2084-92.)

Dr. Mitscher, however, suggested that the resolution of the ofloxacin enantiomers would be a routine matter. (See, e.g., Mitscher Tr. at 606.) Although he did not specifically explain how the prior art taught the application of known resolution methods to quinolones such as ofloxacin, he correctly observed that the prior art referenced every basic method applied by Daiichi researchers in Processes A, B and C. (See generally id. at 610-39.)

Other evidence presented at trial demonstrated that the prior art sufficiently enabled the resolution of ofloxacin enantiomers. Notably, within months after Daiichi researchers first separated the enantiomers, at least four other companies succeeded in obtaining levofloxacin, using the same methods as Daiichi. (PX

382/T at DAI-0135390.) Moreover, during the prosecution of the '407 patent, the Examiner initially rejected the claims to levofloxacin on the basis that "[t]o resolve and identify the more active isomer is held to be within the skill of the worker in the art." (DX 8 at 69.) Daiichi never substantively challenged this conclusion by the Examiner. (See id. at 77-83, 201-08.)

The Court is also not convinced that Daiichi's difficulties in resolving ofloxacin's enantiomers establish that the prior art was not enabling. The researchers initially charged with the project had no prior lab experience with enantiomeric separation at Daiichi. (Hayakawa Tr. at 4354-55.) Moreover, Daiichi did not make a focused, sustained effort to resolve ofloxacin's enantiomers until April of 1984, when Dr. Hayakawa was appointed supervisor of the quinolone group. (Id.; see id. at 3915-16.)

The Court remains mindful that a person of ordinary skill in the art is "not one who undertakes to innovate, whether by patient, and often expensive, systematic research or by extraordinary insights." Standard Oil Co., 774 F.2d at 454. Nonetheless, such a rule does not require the Court to restrict the ability of hypothetical skilled artisans to only following explicit research blueprints; otherwise, there would be no need to consider whether sufficient motivation or reason existed to combine references. Here, the evidence indicates that the separation of ofloxacin's

enantiomers was a logical extension of the prior art, not an innovation. Although the Court does not agree that the enantiomeric resolution would be a routine matter to a person of ordinary skill in the art, it nevertheless finds that the prior art sufficiently enables the resolution.

iii. Reasonable Likelihood of Obtaining Levofloxacin

Mylan fails, however, to prove by clear and convincing evidence that a skilled artisan would reasonably expect levofloxacin to exhibit its unique combination of properties. Levofloxacin is twice as potent, about ten times more soluble, and appreciably less toxic than ofloxacin. As a result, the drug also has better pharmacokinetics and lower levels of bacterial resistance. (Zhanel Tr. at 4863-64; PX 3083.) Thus, levofloxacin is pharmaceutically superior to ofloxacin in virtually every relevant aspect.

Of course, as Mylan observes, the prior art suggests that one of the enantiomers is often more active and soluble than its racemate. (See, e.g., DX 359; DX 463.) According to Dr. Mitscher, however, it is difficult to improve upon one property of an antibiotic without sacrificing another property. (Mitscher Tr. at 1150.) In a publication appearing after the invention of levofloxacin, Mitscher wrote:

> Rarely can optimization of a single characteristic be achieved except at the partial expense of one of the other desired characteristics. Consequently, all antibiotics presently marketed represent the product of a series of painful compromises. Thus, the chemist is often faced with the necessity of deciding which characteristics are most important and at present one of these certainly is overcoming microbial resistance.

(PX 3505 at 269.)

Furthermore, Dr. Rodricks testified that increased activity generally correlates with increased toxicity. (Rodricks Tr. at 4646.) The prior art on which Mylan relies fails to contradict this general rule. (DX 359 (the "Ariëns article"); DX 407 (the "Haley article").) The Ariëns article does not assert that the "therapeutic isomer" will not also have a higher toxicity; indeed, it did not compare the relative toxicities of the isomers. Instead, the article suggests that the inactive isomer "may very well contribute to the side-effects." (DX 359 at MYL-OM-44285) (emphasis added). The Haley article, which Mylan erroneously cites to disprove the general rule, concludes that the most potent enantiomer of a racemic compound is also the most toxic. (DX 407 at 212.) Thus, compared to the typical antibiotic, levofloxacin represents the unusual case in which each of its desired properties is superior to (if not considerably superior to) those of its predecessor. Cf. Adamson, 275 F.2d at 953 (noting that the more

active enantiomer of a particular racemate was more toxic than the other enantiomer and the racemate itself).

Moreover, a skilled artisan could not have reasonably expected the degree of activity exhibited by levofloxacin. Although the prior art certainly indicates that one enantiomer is often more therapeutically active than the other, it does not teach that the more active enantiomer is consistently twice as potent as the racemate. To the contrary, the articles cited by Mylan suggest a range of possible therapeutic activity ratios. (See DX 370 at 86; DX 359 at MYL-OM-44285 ("In certain cases the differences in activity of the isomers, the enantiomers, are scientifically established, but in many cases this knowledge is lacking.").) Indeed, the enantiomers studied in the Haley article had similar potencies. (DX 407 at 212.) Moreover, the Gerster abstract does not suggest that the S(-) enantiomer of flumequine possessed all of the antibacterial activity of the racemate. Thus, the evidence establishes that levofloxacin's relative antimicrobial activity would have been considered a possibility, but not a reasonable expectation.

Mylan has not demonstrated that a skilled artisan would reasonably have expected to obtain levofloxacin, considering the

invention "as a whole" in light of the prior art. 35 U.S.C. § 103(a). This failure alone is fatal to Mylan's obviousness defense, provided that an enantiomer is not prima facie obvious.

iv. Unexpected Results

Even if Mylan had successfully established a prima facie case (via structural similarity or otherwise), the surprising properties and advantages of levofloxacin are strong evidence of nonobviousness. "Evidence that a compound is unexpectedly superior in one of a spectrum of common properties . . . can be enough to rebut a prima facie case of obviousness." In re Chupp, 816 F.2d 643, 647 (Fed. Cir. 1987) (citation omitted).

The most remarkable quality of levofloxacin is its solubility, which is approximately ten times greater than that of ofloxacin. Before June, 1985, the largest reported difference in solubility between an enantiomer and its racemate was five-fold. (DX 463 at 238; DX 428 at 636.) Solubility expert Dr. Myerson also opined that the relative difference in solubility between levofloxacin and ofloxacin was "very unexpected."[22] (Myerson Tr. at 4106-07.) Therefore, the Court finds that levofloxacin's increased solubility

[22] Based on a review of the relative solubilities of enantiomers in the prior art, Dr. Myerson testified that one of ordinary skill in the art would have reasonably expected levofloxacin to be one to two times more soluble than ofloxacin, at most. (Myerson Tr. at 4142-43.)

was a substantial improvement over ofloxacin, and, thus, an unexpected result.

Although the prior art suggests that levofloxacin's relatively higher activity and lower toxicity were not surprising in themselves, the combination of those properties would have been unexpected. As already noted, increased therapeutic activity is normally accompanied by increased toxicity. This correlation was (and is) considered a "major impediment" to successful drug design. (Rodricks Tr. at 4646.) Moreover, an article authored by Dr. Gerster reporting on the relationship between the activity and toxicity of a flumequine analogy suggests the unexpectedness of levofloxacin's therapeutic index, i.e., the difference between its therapeutic and toxic effects. (PX 759; Rodricks Tr. at 4848-52.) The publication, written while the '407 patent was pending, recognized the "important impact on further synthesis of tricyclic quinolone antibacterials" that would result if one could simultaneously decrease side effects while increasing antibacterial activity. (PX 759 at 87.) Dr. Gerster reported, however, that, "unfortunately," the side effects and activity moved in parallel; therefore, he concluded that "the use of an optically pure tricyclic quinolone antibacterial would not lead to significant decrease in or elimination of CNS stimulation as a side effect."

(Id. at 93.) The example of levofloxacin proves otherwise. Thus, levofloxacin's higher therapeutic index would have been unexpected.

Levofloxacin's effectiveness against the S. pneumoniae bacteria also would have been unexpected. At its approved dosage of 500 mg once-a-day, levofloxacin achieves an AUC_{24}/MIC ratio[23] of 35 against S. pneumoniae. (PX 3238.) In contrast, ofloxacin achieves an AUC_{24}/MIC ratio of only 19.5 against S. pneumoniae at a total dosage of 800 mg (two 400 mg dosages) per day. (Id.) Moreover, although bacterial resistence is an inevitability for any anti-infective (DX 905A), levofloxacin has exhibited an unusually lower potential to "select" for quinolone-resistant S. pneumonia than an equally potent amount of ofloxacin. (PX 3083) (1999 study authored by H.B. Drugeon et al.) The researchers who observed this difference were only able to speculate as to its cause. (Id. at 58) ("It is difficult to understand why ofloxacin and ciprofloxacin selected Type 2 mutants while levofloxacin did not.") Dr. Zhanel, chair of the Antibiotic Resistance Research Group in Medicine at the University of Manitoba, Canada, also stated that levofloxacin's

[23] "AUC" denotes "area under the curve." AUC_{24} is "essentially the total amount of drug in the blood after a 24 hour period," (Zhanel Tr. at 4846-47), and, as previously discussed, MIC, or "minimum inhibitory concentration," is a measure of drug potency. The AUC_{24}/MIC ratio, therefore, "correlates directly" with a drug's (particularly a quinolone's) ability to kill bacteria. (Id. at 4850-52.) A higher AUC_{24}/MIC ratio indicates greater effectiveness at killing bacteria, as opposed to merely inhibiting their growth. (Id.)

relative potential to select for resistence was "unexpected." (Zhanel Tr. at 4890-91.)

c. Secondary Considerations

Secondary considerations, also known as indicia of nonobviousness, "must be considered in determining obviousness." Ruiz, 234 F.3d at 667 (citations omitted). Indeed, such objective indicia may be "the most probative and cogent evidence in the record." Stratoflex, 713 F.2d at 1538.

i. Commercial Success

"The commercial response to an invention is significant to determinations of obviousness, and is entitled to fair weight." Demaco Corp. v. F. Von Langsdorff Licensing Ltd., 851 F.2d 1387, 1391 (Fed. Cir. 1988). In J.T. Eaton & Co. v. Atlantic Paste & Glue Co., 106 F.3d 1563 (Fed. Cir. 1997), the Federal Circuit offered an incisive summary of the commercial success analysis:

> [T]he asserted commercial success of the product must be due to the merits of the claimed invention beyond what was readily available in the prior art. When a patentee can demonstrate commercial success, usually shown by significant sales in a relevant market, and that the successful product is the invention disclosed and claimed in the patent, it is presumed that the commercial success is due to the patented invention. If a patentee makes the requisite showing of nexus between commercial success and the patented invention, the burden shifts to the challenger to prove that the commercial success is instead due to other factors extraneous to the patented invention, such as advertising or superior workmanship.

Id. at 1571 (citing Richdel, Inc. v. Sunspool Corp., 714 F.2d 1573, 1580 (Fed. Cir. 1983) and Demaco Corp., 851 F.2d at 1392-93).

The patented invention in this case has indisputably enjoyed extraordinary commercial success. Since its launch in 1997 and through 2003, levofloxacin products (sold as LEVAQUIN) have generated approximately $5 billion in sales and more than $1 billion in profit for Ortho. (Stewart Tr. at 5891, 5893-94, 5914-15; PX 3520.) During that period, annual sales of LEVAQUIN have risen from $170 million (adjusted for inflation) in 1997 to more than $1 billion in 2003. (Id. at 5891, 5894-96; PX 3257A; PX 3363A.)

Since the successful product is the invention disclosed and claimed in the patent, Mylan bears the burden of showing that levofloxacin's commercial success is due to extraneous factors. To meet its burden, Mylan presented voluminous evidence of "exogenous forces," including delays in FDA regulatory approval, changes in FDA clinical studies requirements, unanticipated emergence of a new competing class of anti-infectives, subsequent development of resistance in that class, Ortho's lack of prior anti-infectives experience, FDA-approved indications, ongoing clinical development, publication strategy, pricing, rebates and discounts, samples, product positioning, sales force size and quality, investment in brand marketing expenses ("BME"), thought leader development,

microbiological support, formulary access, and managed care strategy. Most of these forces involve deliberate marketing strategies by Ortho; the remaining forces relate to the medical and regulatory context in which levofloxacin has been sold.

To be sure, numerous factors--perhaps even all those cited by Mylan--contributed in part to levofloxacin's profits. The weight of all of that evidence, however, does not lead to the conclusion Mylan advocates, that "exogenous forces" sever the nexus between the merits of levofloxacin and its commercial success. The ultimate success of a prescription antibiotic hinges on its clinical properties. (Hooper Tr. at 1581.) Here, the evidence reflects a fairly extensive recognition among doctors and hospitals that levofloxacin is not only an effective drug but also is clinically distinguishable from ofloxacin. (See, e.g., Zhanel Tr. at 4841-43, 4895; Johnson Tr. at 5431; Nelson Tr. at 3539-43.)

Moreover, Ortho did not devote an unusual amount of resources to marketing. When levofloxacin was introduced, Ortho's sales force was among the smallest in the anti-infective market. (Fischer Tr. at 5621-22.) Ortho also launched its marketing efforts based solely on the FDA-approved package insert, instead of including other promotional materials, as was the norm in the industry. (See Johnson Tr. at 5426-27.) Furthermore, BME figures for LEVAQUIN in its first year on the market were comparable to

that of ofloxacin (marketed as FLOXIN) for the year of its launch. (PX 3086.) LEVAQUIN also maintained a relatively low ratio of total sales to promotional expenditures as compared to competing respiratory anti-infectives. (PX 3277.)

Ortho's marketing of LEVAQUIN vis-a-vis FLOXIN also fails to explain levofloxacin's remarkable commercial success. Following its launch in 1991, FLOXIN never achieved more than 4.5% penetration of the revenue share in the oral anti-infective market. (PX 3253A.) In contrast, after just its second year on the market, LEVAQUIN had garnered more than 5% of the revenue share and had captured almost 14.5% of the total revenue share by the end of 2002. (Id.) Similarly, in the market for competing oral quinolones, FLOXIN's largest share of total prescriptions never exceeded 20%; LEVAQUIN, by contrast, had captured nearly 40% of that market by the end of 2002. (PX 3254; PX 3254A; PX 3255; PX 3256.) In the competing i.v. quinolone market, LEVAQUIN's largest revenue share exceeded 65% in 2000; FLOXIN's never surpassed 25%. (PX 3260.)

In summary, the Court is unpersuaded by Mylan's exogenous forces arguments. In the competitive anti-infective market, the overwhelming response by doctors and hospitals to levofloxacin cannot be attributed exclusively to clever marketing strategies and "a perfect storm" of unforeseen FDA delays and regulatory changes.

Levofloxacin was a commercial success on its own merits, a factor which weighs in favor of nonobviousness.

ii. Near Simultaneous Invention

Near simultaneous invention by two or more inventors is an indicium of obviousness. Ecolochem, Inc. v. Southern Cal. Edison Co., 227 F.3d 1361, 1379 (Fed. Cir. 2000) (quotations omitted). As evidence of near simultaneous invention, Mylan noted the levofloxacin synthesis method invented by Drs. Mitscher and Chu in late 1985 or early 1986. It also presented a book chapter written by Dr. Hayakawa indicating that four companies--Abbot, Bayer, Dainippon and Kyorin--reported the synthesis of levofloxacin six months after the Daiichi inventors did so, using the same resolution methods. (PX 382/T at DAI-0135390; see also DX 942/T, DX 152/T) However, the parties presented no corroborating evidence as to the precise dates of the competing companies' reported levofloxacin synthesis. Thus, the Court is unable to determine whether those companies were motivated by Dr. Hayakawa's published description of levofloxacin's properties and general resolution methodology in January 1986. (PX 907.) Consequently, the Court finds that Mylan's evidence of near simultaneous invention moderately weighs in favor of a finding of obviousness.

iii. Fulfillment of Long-Felt Need

Whether an invention fulfilled a long-felt need is evidence of nonobviousness. The patented product must solve a long-felt need before other products do so. See Monarch Knitting Mach. Corp. v. Fukuhara Indus. & Trading Co., Ltd., 139 F.3d 877, 884 (Fed. Cir. 1998). Thus, courts should consider whether "contemporaneous development" met the need first. Id. A long-felt need also must have objectively existed in fact. In re Gershon, 372 F.2d 535, 538 (C.C.P.A. 1967); see also Orthopedic Equip. Co., Inc. v. All Orthopedic Appliances, Inc., 707 F.2d 1376, 1382 (Fed. Cir. 1983). Evidence of the existence of a long-felt need may be found, among other places, in the prior art, Gershon, 372 F.2d at 538, or in the patent itself. Amazon.com, Inc. v. Barnesandnoble.com, Inc., 239 F.3d 1343, 1366 (Fed. Cir. 2001).

Daiichi/Ortho asserts that levofloxacin fulfilled a long-felt need for a broad-spectrum quinolone that safely and effectively treated respiratory infections. Mylan, however, contends that ofloxacin had already met that need and that, regardless, the need always exists for safer and more effective antibiotics.

Daiichi/Ortho presented significant evidence of numerous failed attempts to develop safe and effective quinolones generally (e.g., PX 4101), and of the need for a "respiratory quinolone"

specifically. (E.g., PX 3118A at MYLOM-06073.) For example, in 1993, a leading treatise on quinolones noted the shortcomings of available quinolones (including ofloxacin) to treat respiratory infections effectively, explaining that "[t]he use of fluoroquinolones in the treatment of respiratory tract infections continues to engender controversy . . . . [T]he effectiveness of the currently available agents against gram-positive respiratory pathogens, particularly S. pneumoniae, is less than optimal." (PX 787A at 531-32.) Thus, the medical and scientific communities recognized a persistent need for a quinolone that could safely and effectively combat gram-positive respiratory pathogens, such as S. pneumoniae. The Court finds that levofloxacin fulfilled that need in light of the drug's demonstrated effectiveness against S. pneunomiae.

The need at issue can only be fulfilled temporarily, however. In the context of modern medicine, whether any antibiotic can fulfill or solve a long-felt need presents a novel legal issue because such drugs are inevitably rendered less effective by drug resistant strains of bacteria. Pharmaceutical researchers are now undoubtedly attempting to develop, and likely will develop, a drug that is superior to levofloxacin. Indeed, Ortho's Anti-Infective Scientific Advisory Board discussed the potential replacement of LEVAQUIN before the filing of this litigation. (See DX 1512.) In

light of these scientific realities, the Court finds that, to the extent that levofloxacin met a long-felt need, it cannot permanently solve that need. Therefore, although this factor supports a finding of non-obviousness, it carries only modest weight in the Court's analysis.

iv. Prior Failure

Daiichi/Ortho contends that its inventors' failed attempts to produce the claimed invention are probative of nonobviousness. In the context of secondary considerations, the Federal Circuit has generally focused on the prior failures of others in the industry, not the inventors. See, e.g., Advanced Display Sys. v. Kent State Univ., 212 F.3d 1272, 1285 (Fed. Cir. 2000). Moreover, the Court has already weighed Daiichi's inventive struggles in evaluating whether a skilled artisan would have a reasonable expectation of success in obtaining levofloxacin. Accordingly, there is no need to reconsider Daiichi's unsuccessful efforts in resolving the enantiomers of ofloxacin.

v. Mylan's Choice to Copy Levofloxacin

"The copying of an invention may constitute evidence that the invention is not an obvious one. This would be particularly true where the copyist had itself attempted for a substantial length of time to design a similar device, and had failed." Vandenberg v.

Dairy Equip. Co., 740 F.2d 1560, 1567 (Fed. Cir. 1984); see Advanced Display Sys., 212 F.3d at 1285-86.

The '892 Patent, which covers ofloxacin, expired on August 2, 2003. Notwithstanding the expiration of the ofloxacin patent and Mylan's insistence that ofloxacin and levofloxacin are virtually indistinguishable, Mylan chose to file an ANDA only for levofloxacin. (Owens Tr. 173-74.) Additionally, Mylan owned the rights to market another fluoroquinolone, sparfloxacin, which it attempted to market as ZAGAM. (Id. at 168; PX 4101.) Despite the early promise of sparfloxacin as a respiratory quinolone, its use was limited because of phototoxicity and Qtc prolongation concerns. (PX 3118A at MYLOM-060673; PX 4101; Mitscher Tr. at 1156-57.)

In choosing to copy levofloxacin, Mylan asserts that it did not consider the compound's properties. It argues that it decided to pursue an ANDA because levofloxacin (a) was sold in tablet form; (b) was manufacturable within Mylan; (c) presented a "good business opportunity"; (d) was available from a quality raw material supplier; and (e) provided a first-to-file Paragraph IV opportunity for exclusivity. (Owens Tr. at 153.)

Despite this rationale, it is difficult to believe that Mylan would produce a generic drug without heavily weighing its respective properties. Mylan's asserted decision-making process otherwise begs an important question: Why did producing

levofloxacin present a "good business opportunity"? The earlier analysis of levofloxacin's relative properties and commercial success provides an obvious answer--levofloxacin is demonstrably superior to ofloxacin. Thus, the Court finds that Mylan's decision to copy LEVAQUIN instead of FLOXIN is significant evidence of non-obviousness, particularly in light of Mylan's lack of success in marketing its own respiratory quinolone.

vi. Third Party Praise and Awards for Levofloxacin

"Another indicia of non-obviousness of a product is the acclamation it receives when it is released." Ecolochem, 227 F.3d at 1380; see also Vulcan Eng'g Co. v. FATA Aluminium, Inc., 278 F.3d 1366, 1373 (Fed. Cir. 2002) ("Appreciation by contemporaries skilled in the field of the invention is a useful indicator" of nonobviousness.) Daiichi and Dr. Hayakawa have received awards from industry and government for the invention of levofloxacin. They both received the Molecular Chirality Award for the invention of levofloxacin and ofloxacin. (Hayakawa Tr. at 3907-09; PX 387T.) Dr. Hayakawa, in particular, was recognized by the Pharmaceutical Society of Japan for the invention of levofloxacin, which was characterized as a "breakthrough drug." (Hayakawa Tr. at 3906-07.) In 2001, Dr. Hayakawa was given the Education Science Minister Award for his work on levofloxacin and ofloxacin. (Id. at 3908-09; PX 3251; PX 386.) Finally, the Emperor of Japan awarded the

prestigious purple ribbon medal--for outstanding contribution to scholarship or the arts--to Dr. Hayakawa for his invention of levofloxacin. (Hayakawa Tr. at 3909-10; PX 3250.) Mylan suggests, but fails to prove, that all of these awards are primarily attributable to Dr. Hayakawa's development of ofloxacin. Thus, these recognitions support a finding of nonobviousness.

vii. Skepticism of Persons Skilled in the Art

Expressions of skepticism by those in the art are "relevant and persuasive" evidence of nonobviousness. Monarch Knitting Mach. Corp. v. Sulzer Morat GmbH, 139 F.3d 877, 885 (Fed. Cir. 1998) (citation omitted); see also Ruiz, 234 F.3d at 668 ("Proceeding contrary to the accepted wisdom . . . is 'strong evidence of unobviousness.'") (quotation omitted). Under this factor, Daiichi/Ortho offers Dr. Gerster's article that concluded "the use of an optically pure tricyclic quinolone antibacterial would not lead to significant decrease in or elimination of CNS stimulation as a side effect." (PX 759 at 93.) As Mylan notes, however, Gerster's article was published in 1989, four years after the date of the invention. Thus, the article is not prior art and could not have discouraged the inventors from attempting to resolve the enantiomers of ofloxacin. As such, the article is not relevant with respect to the skepticism factor as conceived by the Federal Circuit. See Monarch Knitting, 139 F.3d at 885.

viii. Licensing

"Licenses taken under the patent in suit may constitute evidence of nonobviousness; however, only little weight can be attributed to such evidence if the patentee does not demonstrate 'a nexus between the merits of the invention and the licenses of record.'" In re GPAC, 57 F.3d 1573, 1580 (Fed. Cir. 1995) (quotation and citation omitted). Daiichi licensed its levofloxacin patent internationally to three major pharmaceutical companies: Ortho-McNeil/Johnson & Johnson, Glaxo and Hoechst. These companies, however, also owned licenses to ofloxacin, a drug which had already established itself as a competitor in the anti-infective market. Mylan offered evidence suggesting that these companies bought licenses for levofloxacin due its extended patent life, among other reasons. (See, e.g., Jarosz Tr. at 5855.) Daiichi/Ortho otherwise fails to show that licenses were sought because of the merits of levofloxacin. Thus, the Court places nominal, if any, weight on licensing in the obviousness analysis.

d. Conclusion on the Obviousness Defense

After weighing all of the evidence on the issue of obviousness, the Court concludes that Mylan has failed to meet its burden of proof. If enantiomers are not prima facie obvious in light of their racemates, Mylan cannot meet its prima facie burden of showing, by clear and convincing evidence, that a person of

ordinary skill in the art would have had a reasonable expectation of success in producing levofloxacin. Otherwise, the Court finds that levofloxacin's demonstrably unexpected results alone successfully rebut a prima facie case of obviousness, if so established by the enantiomer per se or structural similarity. The trial evidence of other secondary considerations, taken as a whole, also confirms and bolsters the Court's conclusion that Mylan has not proven, by clear and convincing evidence, that the '407 patent is obvious.[24]

C. Inherent Anticipation

1. Legal Standard & Background

"Anticipation is a question of fact . . . ." Merck & Co., Inc. v. Teva Pharms. USA, Inc., 347 F.3d 1367, 1369 (Fed. Cir. 2003). To prevail on an anticipation defense, a defendant must prove by clear and convincing evidence that every limitation of a plaintiff's asserted claims was contained, either expressly or

[24] On December 6, 2004, counsel for Mylan submitted a recent Canadian court opinion finding that a patent challenger's allegation of obviousness against levofloxacin was "justified." Janssen-Ortho Inc. v. Novopharm Ltd., [2004] F.C. 1631 (Ottawa, Ontario). The Court finds the Janssen-Ortho decision unpersuasive and largely inapposite for a multitude of reasons: (1) it was not a final decision; (2) it imposed a lower burden of proof, i.e., "a balance of the probabilities"; (3) it applied a significantly different test for obviousness that most notably failed to weigh secondary considerations of non-obviousness; (4) it based its conclusion on limited testimonial evidence and an extremely truncated review of the prior art; (5) it focused on levofloxacin's properties in isolation; and (6) it is a foreign, non-authoritative case.

inherently, in a single prior art reference. Union Carbide Chems. & Plastics Tech. Corp. v. Shell Oil Co., 308 F.3d 1167, 1188 (Fed. Cir. 2002). A prior art reference may anticipate without disclosing a feature of the claimed invention if that missing characteristic is necessarily present, or inherent, in the single anticipating reference. Schering Corp. v. Geneva Pharms., 339 F.3d 1373, 1377 (Fed. Cir. 2003), reh'g en banc denied, 348 F.3d 992 (Fed. Cir. 2003). "Anticipation does not require the actual creation or reduction to practice of the prior art subject matter; anticipation requires only an enabling disclosure." Id. at 1380.

The Federal Circuit has recognized for a number of years that a person may infringe a claim to a metabolite if the person ingests a compound that metabolizes to form the metabolite. Id. (citing Hoechst-Roussel Pharms., Inc. v. Lehman, 109 F.3d 756, 759 (Fed. Cir. 1997), and Zenith Labs., Inc. v. Bristol-Myers Squibb Co., 19 F.3d 1418, 1421-22 (Fed. Cir. 1994)). "An identical metabolite must then anticipate if earlier in time than the claimed compound." Id. Schering expanded the law of inherent anticipation, holding that a compound that necessarily forms in the body is anticipated by another compound intended for use in the body regardless of whether persons of ordinary skill in the art recognized that the compound was a metabolite of the earlier compound. Id. at 1377.

Schering involved the issue of whether a claim to the compound descarboethoxyloratadine ("DCL") was invalid as anticipated by the patent to loratadine (the chemical name for Claritin). Id. at 1375. The claims at issue were construed to cover DCL in all its forms, including "metabolized within the human body" and "synthetically produced in a purified and isolated form." Id. at 1376. The Federal Circuit found that it was established at the time of the litigation that "DCL necessarily and inevitably forms from loratadine under normal conditions . . . [and] is a necessary consequence of administering loratadine to patients." Id. at 1378. That conclusion was confirmed by "the extensive record evidence of testing done on humans to verify the formation of DCL upon ingestion of loratadine." Id. at 1379. That fact was unknown, however, at the time the loratadine patent issued.

The Federal Circuit nonetheless concluded that DCL was anticipated by the disclosure of the administration of loratadine to humans, a process that inevitably results in the formation of DCL. Id. at 1380. The fact that its formation was unappreciated did not factor in the analysis; the key was that the product of practicing the earlier invention was the same compound as the later claimed invention. Id.

Mylan asserts that Schering directly governs this case because clear and convincing evidence establishes that, when ingested, ofloxacin in vivo inevitably becomes levofloxacin as claimed in the '407 patent. According to Mylan, levofloxacin is therefore inherently anticipated by ofloxacin. Daiichi/Ortho, however, maintains that, unlike Schering, there is no clear and convincing evidence that levofloxacin is formed in the body. Daiichi/Ortho further argues that, even if free levofloxacin molecules exist in vivo, there is no evidence that levofloxacin as claimed in the '407 patent is formed in vivo.

Although Mylan staked its case on its assertion that monomers of the levorotatory enantiomer formed upon the ingestion of ofloxacin, and that the formation produced levofloxacin as claimed in the '407 patent, it failed to prove the science by clear and convincing evidence. Moreover, in this Court's opinion, it was proving the wrong science, as a monomer of levofloxacin would not anticipate the claims of the '407 patent.

2. Evaluation of the Science

Two of Daiichi/Ortho's experts, Drs. Myerson and Wentland, admitted that free molecules of levofloxacin, or "monomers," likely exist in solution. Its third expert, Dr. Zhanel, testified that there is "no evidence that monomers, dimers or higher order aggregates exist in the human body after you administer ofloxacin."

(Zhanel Tr. at 6520.) Although the concessions from Drs. Myerson and Wentland at first appear promising to Mylan's cause, on closer inspection they lack the evidentiary weight necessary to support a conclusive determination of what happens when ofloxacin is ingested.

Mylan, through Dr. Mitscher, relied on three principal pieces of evidence in support of its levofloxacin formation theory: the Kumamoto study, the Shen Model,[25] and Lipinski's Rules.[26] Daiichi/Ortho's experts methodically attacked the reliability of each of these sources as support for the Court's scientific conclusion.

Mylan asserts that various studies comparing the serum and renal clearance rates for enantiomers after the administration of ofloxacin prove that readily detectable amounts of levofloxcacin must exist separately in vivo. (Mitscher Tr. at 863-79; DX 453; DX 980; DX 72.) Specifically, Mitscher testified that the dextrorotatory enantiomer is cleared from the blood and through the urine more quickly than the levorotatory enantiomer. (Mitscher Tr. at 6642-43.)

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[25] The Shen Model is a model used identify how quinolones behave in solution and at the DNA binding site. (Mitscher Tr. at 6191.)

[26] Lipinski's Rules refer to principles of pharmaceutical chemistry that are normally applied in early stages of drug research to predict the ability of a drug to penetrate into cells by passive diffusion. (Mitscher 6410-11; id. at 6595.)

Dr. Zhanel however, referred to contrary studies (PX 3083K; PX 3000; PX 3083FF) to support his opinion that, after administration of ofloxacin, the enantiomers remain in the body in one-to-one ratios in the serum, urine and tissue. (Zhanel Tr. at 6425-71.?) Most significantly, Zhanel testified at length about a peer-reviewed publication authored by A.R. Gascon et al., entitled "Pharmocodynamics of Ofloxacin Enantiomers after Intravenous Administration for Antibiotic Prophylaxis in Biliary Surgery" (the "Gascon article"). (PX 3083K; Zhanel Tr. at 6427.) Zhanel considered the Gascon article superior to the articles on which Mitscher had relied because it involved clinical patients, was the largest relevant study available, and was the only study that assessed serum, urine and tissue. (Zhanel Tr. at 6427-30.) Based on that article, Zhanel concluded that the clearance rates of the ofloxacin enantiomers vary slightly, but will converge toward a 1:1 ratio. (Id. at 6437.)

Because of the conflicting expert testimony at trial, Mylan failed to prove that the ratio of the ofloxacin enantiomers varied in vivo to a sufficient degree that the Court could reliably conclude they existed independently in vivo. Drs. Mitscher and Zhanel offered two reasonable, conflicting interpretations of the science. Although a definitive scientific resolution may be a goal

for future research, the lack of agreement on the matter at this time precludes its resolution in a court of law.

Mylan next relies on the Kumamoto in vitro studies. Although commissioned by Daiichi, the Kumamoto studies were neither published nor peer-reviewed. Furthermore, according to Dr. Myerson, they were based on "flawed assumptions," "crude" equations, and poor data. (Myerson Tr. at 6300.) Myerson explained these criticisms at length, and opined that no chemist or chemical engineer familiar with the Kumamoto studies would rely on them to conclude that ofloxacin molecules necessarily and inevitably exist as monomers in solution. (Myerson Tr. at 6300-14.)

With respect to the Shen Model, although Dr. Mitscher did not waiver from his belief in its accuracy, he admitted that it is a "hypothesis" and conceded that it is unknown whether it forecasts what actually happens at the enzyme binding level. (DX 441; Mitscher Tr. at 6210-11.) Furthermore, the Shen Model is the subject of some controversy and competing hypotheses in the scientific community. (Mitscher Tr. at 6213-19; PX 5071; PX 5059; PX 5058; PX 5060; PX 5076; PX 5063.)

Finally, with respect to Lipinski's Rules, the Court was presented with conflicting and inconsistent evidence. Mitscher asserted that the Rules apply and indicated that levorotatory

enantiomers exist as monomers, or ofloxacin would not be an effective drug. (Mitscher Tr. at 6595-97.) Lipinski's Rules, however, have never been used to illustrate the proposition Mylan advances here. As Mitscher admitted, they have never been applied to determine whether an already-marketed drug exists as a monomer or dimer in the human body. (Id. at 6620.) Given this dispute, the Court cannot conclude that levorotatory enantiomers exist as monomers in vivo.

3. Anticipation of the Claims as Limited

The inherent anticipation inquiry turns in large part on the claim construction. In Schering, the issue was easily framed because the claim construction covered the compound in all its forms, including in vivo production. Thus, for loratadine to become what was claimed it needed only to become the compound DCL "in readily detectable amounts."

In the case at bar, both disputed claims require optical activity and substantial purity, and claim 5 further requires that an "antimicrobially effective amount" of levofloxacin be present. Therefore, detection of free molecules of the levorotatory enantiomer following digestion of ofloxacin is not enough to anticipate levofloxacin as claimed in the '407 patent. Under Schering, optically active and substantially pure levofloxacin must be formed in vivo before ofloxacin can anticipate.

The post-Schering case of Novartis Pharmaceuticals Corp. v. Eon Labs, 363 F.3d 1306 (Fed. Cir. 2004), is instructive in this regard. In Novartis, the court construed the claim of a "hydrosol" of a given compound to be limited to something synthetically prepared, a "medicinal preparation." Id. at 1311. Thus, even though the claimed compound was formed in vivo when a previously patented compound was ingested, the claim was not anticipated because production of the compound inside the body did not form the compound with the additional synthetic preparation limitation. Id. at 1311-12 (distinguishing the case from Schering on the basis that there was "no agreement that the claim encompasses the product formed after ingestion").

At most, the evidence at trial established that, as an empirically unconfirmed theory, the ingestion of ofloxacin will produce free monomers of the levorotatory enantiomer. Whether the monomers exist in any substantially pure or optically active concentration is, however, only a working hypothesis at this stage of the science.

4. Conclusion on Inherent Anticipation

At trial, the Court heard conflicting testimony as to whether, based on the scientific publications available at the time of trial, there was sufficient evidence to opine on whether levorotatory and dextrorotatory enantiomers separated or remained

associated after ofloxacin was ingested. None of the scientists who testified was able to present peer-reviewed articles or scientific studies that actually reported the detection of free levofloxacin molecules in vivo. More importantly, there was no evidence that levofloxacin as claimed in the '407 patent is produced when ofloxacin is ingested. Thus, even had the Court been presented with sufficient evidence to evaluate the proposed novel applications of the Shen Model and Lipinski's Rules, Mylan still could not meet its burden. Because there is no proof to a reasonable certainty that, as a matter of scientific fact, optically active levofloxacin exists in vivo after ofloxacin is ingested, Mylan has failed to prove inherent anticipation by clear and convincing evidence.

V. CONCLUSION

The Court concludes that Mylan fails to prove, by clear and convincing evidence, that the '407 patent is invalid due to prior invention, indefiniteness, inequitable conduct, obviousness or inherent anticipation. In light of Mylan's undisputed infringement, the Court **DECLARES** that making, using, selling, offering to sell, or importing the levofloxacin tablets described in ANDA Nos. 76-276 & 77-097 or bulk levofloxacin for use in manufacturing such tablets constitutes infringement of the '407 patent. The Court thus **ENJOINS** Mylan, its officers, agents,

servants and employees from making, using, offering to sell, selling, or importing the levofloxacin tablets described in ANDA Nos. 76-276 & 77-097 or bulk levofloxacin for use in manufacturing such tablets. The Court also **ORDERS** that the effective date of the products described in ANDA Nos. 76-276 & 77-097 shall not precede the expiration of the '407 patent.

It is so **ORDERED**.

The Clerk is directed to transmit copies of this Order to counsel of record herein.

DATED: December 23, 2004.

IRENE M. KEELEY
UNITED STATES DISTRICT JUDGE