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No. 2009-1362

In the
United States Court of Appeals
for the Federal Circuit

ORTHO-MCNEIL PHARMACEUTICAL, INC.,
and ORTHO MCNEIL, INC.,

Plaintiffs-Appellees,

and

DAIICHI SANKYO CO., LTD.,

Plaintiff-Appellee,

v.

LUPIN PHARMACEUTICALS, INC.,
and LUPIN LTD.,

Defendants-Appellants.

Appeal from the United States District Court for the District of New Jersey
in case no. 06-CV-4999, Chief Judge Garrett E. Brown, Jr.

BRIEF OF DEFENDANTS-APPELLANTS LUPIN PHARMACEUTICALS, INC. AND LUPIN LTD.

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CERTIFICATE OF INTEREST

Counsel for Defendants-Appellants Lupin Pharmaceuticals, Inc. and Lupin Ltd. certifies the following:

1. The full name of every party or amicus represented by me is:

Lupin Pharmaceuticals, Inc. and Lupin Ltd.

2. The name of the real parties in interest represented by me is:

Lupin Pharmaceuticals, Inc. and Lupin Ltd.

3. All parent corporations and any publicly held companies that own 10 percent or more of the stock of the party or amicus curiae represented by me are:

Lupin Pharmaceuticals, Inc. is a wholly-owned subsidiary of Lupin Ltd. Lupin Ltd. has no parent corporation, and no publicly held company owns 10 percent or more of Lupin Ltd.

4. The names of all law firms and the partners or associates that appeared for the party or amicus now represented by me in the trial court or agency or are expected to appear in this court are:

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Dated: June 3, 2009

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Lupin Pharmaceuticals, Inc. and Lupin Ltd.

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STATEMENT OF RELATED CASES

No other appeal in or from the civil action or proceeding in the lower court has been before this or any other appellate court. Lupin is unaware of any other pending cases that will directly affect or be directly affected by this Court's decision in the pending appeal.

STATEMENT OF JURISDICTION

This action for patent infringement arises under the Patent Laws of the United States, Title 35 of the United States Code. The district court had subject matter jurisdiction under 28 U.S.C. § 1338(a) (patents) because the action involved substantial claims arising under the United States Patent Laws.

This Court has jurisdiction under 28 U.S.C. § 1292(c)(1) (federal court jurisdiction) because subject matter jurisdiction in the district court was based on 28 U.S.C. § 1338 and an order issuing a permanent injunction was entered by the district court.

The district court entered a decision on cross-motions for summary judgment, a final judgment and an order, the latter including entry of a permanent injunction, on April 30, 2009. Lupin Pharmaceuticals Inc. and Lupin Ltd. ("Lupin") timely filed their Notice of Appeal on May 5, 2009.

STATEMENT OF THE ISSUES

1. Whether the patent term extension granted to U.S. Patent No. 5,053,407 ("the '407 patent") under 35 U.S.C. § 156 is valid.

2. Whether a patent term extension granted under the provisions of 35 U.S.C. § 156 is invalid when the basis for the extension was the marketing approval by the U.S. Food and Drug Administration ("FDA") for an enantiomer that has been previously approved for marketing by the FDA as a component in a racemic mixture.

3. Whether it is arbitrary and capricious and/or contrary to law for the FDA to determine that an enantiomer is *not* a newly approved *active ingredient* for purposes of eligibility for five years of FDA new product exclusivity in accordance with 21 U.S.C. §§ 355(c)(3)(E)(ii) and 355(j)(5)(F)(ii), and to subsequently determine that the same enantiomer *is* a newly approved *active ingredient* for purposes of eligibility for a patent term extension under the provisions of 35 U.S.C. § 156, when both statutory provisions use the same term "active ingredient" and both statutory provisions were enacted as part of the same Congressional Act.

4. Whether the scope of the injunction entered by the district court, which enjoins Lupin from making, using, offering to sell, selling or importing the levofloxacin tablets described in Lupin's ANDA or bulk levofloxacin for use in manufacturing such tablets, is improper because it enjoins Lupin from actions for

which the '407 patent no longer provides protection under the limited rights afforded during the Section 156 patent term extension period.

STATEMENT OF THE CASE

Lupin Ltd. seeks approval from the U.S. Food and Drug Administration ("FDA") under the provisions of the Hatch-Waxman Act to sell a generic version of the antibiotic drug levofloxacin, the latter presently marketed as the active ingredient in LEVAQUIN®. U.S. Patent No. 5,503,407 ("the '407 patent") contains claims to the molecule levofloxacin. Prior to the approval of LEVAQUIN® by the FDA, the FDA had approved the drug product FLOXIN®, which contained ofloxacin. Ofloxacin is an active ingredient containing a mixture of equal parts of levofloxacin and its enantiomer. Chemists refer to ofloxacin as a racemate because it contains equal parts of two molecules (referred to as enantiomers), each one being the mirror image of the other.

The sole issue raised in the district court is whether the patent term extension for the '407 patent satisfied the requirement of Section 156(a)(5)(A), *i.e.*, whether "the permission for the commercial marketing or use of the product after such regulatory review period is the first permitted commercial marketing or use of the product under the provision of law under which such regulatory review period occurred." In accordance with 35 U.S.C. § 282, invalidity of the extension of a patent term under 35 U.S.C. § 156 is a defense that may be raised in any action involving the infringement of a patent.

Because there are no genuine issues of material fact, the parties filed cross-motions for summary judgment. The district court granted plaintiffs' motion, denied Lupin's motion, and held that the patent term extension granted to the '407 patent is valid. The court also ordered that Lupin be "enjoined from making, using, offering to sell, selling or importing the levofloxacin tablets described in ANDA No. 78-424 or bulk levofloxacin for use in manufacturing such tablets" and that "the effective date of the products described in 78-424 shall not precede the expiration the expiration of the '407 patent, including all term extensions."

Lupin appeals the denial of Lupin's summary judgment motion and the grant of Plaintiffs' summary judgment motion. Lupin also appeals the scope of the injunction as it extends beyond the scope of the statutory rights that arise as a result of the patent term extension granted to the '407 patent, which patent is now otherwise expired.

STATEMENT OF FACTS

I. FLOXIN® (OFLOXACIN)

Ofloxacin is disclosed and claimed in U.S. Patent 4,382,892 ("the '892 patent"). *A16-A29 at A17, A1189-A1201 at A1190.* The '892 patent issued on May 10, 1983, and is assigned on its face to Daiichi Seiyaku Co., Ltd. *A17, A1190-A1191.*

On December 28, 1990, the FDA approved tablets containing 200 mg, 300 mg and 400 mg ofloxacin under New Drug Application No. 019735 for commercial marketing in the United States. These tablets were marketed in the United States under the trademark FLOXIN®. *A17, A54, A1191.*

Based on the FDA regulatory delay in approving FLOXIN® ofloxacin tablets for marketing in the United States, on December 30, 1991, the USPTO granted an application for patent term extension under 35 U.S.C. § 156, extending the original term of the '892 patent by two years—from September 2, 2001 to September 2, 2003. *A17, A956, A1191.*

The ofloxacin in FLOXIN® is a combination of equal amounts of two chemical compounds called enantiomers. *A17-A18, A1191.* In chemistry, the term "enantiomers" (from the Greek words for "opposite" and "portion") denotes chemical compounds that are mirror images of each other, much as one's left and right hands are "opposite." There are different conventions that may be used to

describe enantiomers. The letters "R" and "S," and symbols "+" and "-," may be used to indicate a particular enantiomer. *A1192.* A combination of enantiomers in equal parts is a racemate. *A17, A1192, Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.,* 348 F. Supp. 2d 713, 721, 724 (N.D.W.V. 2004), *aff'd,* 161 Fed. Appx. 944 (Fed. Cir. 2005).

Since ofloxacin is comprised of levofloxacin and its corresponding enantiomer in equal parts (*A17, A18, A1170, A1193*), the FLOXIN® product, which contained ofloxacin, included both levofloxacin (*i.e.*, (S)(-)ofloxacin) and its enantiomer (*i.e.*, (R)(+)ofloxacin). *A17, A1194, A917, Ortho-McNeil*, 348 F. Supp. 2d at 720-21.

In litigation involving Plaintiffs and the '407 patent, the Plaintiffs agreed that one of the ofloxacin enantiomers, *i.e.*, (S)(-) ofloxacin, is levofloxacin. *A17, A1192-A1193, Ortho-McNeil,* 348 F. Supp. 2d at 724. Plaintiffs further agreed in that same litigation that levofloxacin is one of two biologically active enantiomers present in ofloxacin, and that these enantiomers are present in ofloxacin in a 1:1 ratio. *A17, A1193, Ortho-McNeil*, 348 F. Supp. 2d at 721, 751.

In discussing the "optically active compounds of racemic ofloxacin," the inventors of the '407 patent discuss the biologically active properties of levofloxacin and its corresponding enantiomer:

> the S(-)-compound [*i.e., levofloxacin*] possesses an antimicrobial activity of about 2 times higher than that of the (±)-compound [*i.e., ofloxacin*] and an acute toxicity (LD_{50}) weaker than that of the (±)-compound as determined in mice by intravenous administration. On the other hand, the present inventors found that the R(+)-compound exhibits an antimicrobial activity of only about 1/10 to 1/100 times that of the (±)-compound, whereas it possesses an acute toxicity substantially equal to that of the (±)-compound. That is, the S(-)-form of Ofloxacin [*i.e., levofloxacin*] has been found to have very desirable properties, *i.e.*, increased antimicrobial activity and reduced toxicity, and is expected to be a very useful pharmaceutical agents as compared with the (±)-compound [*i.e., ofloxacin*].

A1196-A1197, A30-A43 at A31.

II. LEVAQUIN® (LEVOFLOXACIN)

On December 20, 1996, the FDA granted marketing approval for injectable and tablet formulations comprising levofloxacin. *A19, A1195.* These levofloxacin formulations have been marketed in the United States under the trademark LEVAQUIN®. *A19, A1195-A1196.*

The '407 patent, which issued on October 1, 1991, discloses and claims the (S)(-) enantiomer of ofloxacin, *i.e.*, levofloxacin. *A18, A19, A1194-A1195, A30-A43.*

After the FDA approved LEVAQUIN®, Daiichi Pharmaceutical Co., Ltd. filed an application seeking an extension of the term of the '407 patent. *A19, A1196.* The U.S. Patent and Trademark Office ("USPTO" or "PTO") granted the

patent term extension, and in doing so extended the term of the '407 patent by 810 days. *A44.* This extension moved the expiration of the '407 patent from October 1, 2008, to December 20, 2010. *A21, A1196, A1087.*

III. THE PRESENT ACTION

The '407 patent is listed in the FDA Orange Book for drugs marketed as LEVAQUIN®. *A1199.*

On July 14, 2006, Lupin Ltd. submitted Abbreviated New Drug Application ("ANDA") No. 78-424 to the FDA seeking approval of levofloxacin tablet formulations. *A21-A22, A1199.*

On September 29, 2006, pursuant to 21 U.S.C. § 355(j)(2)(B)(ii), Lupin Ltd. notified Plaintiffs by letter (this letter being received by Plaintiffs on October 2, 2006) that it had submitted ANDA No. 78-424 to the FDA, and that the application included a Paragraph IV certification with respect to the '407 patent. *A22, A1199.* The Lupin Ltd. certification stated that in its opinion and to the best of its knowledge, Lupin Ltd.'s tablets would not infringe the '407 patent when marketed after October 1, 2008, *i.e.*, after the original (non-extended) expiration date of the '407 patent. *A22, A1199-A1200.*

In response to this notice letter, Plaintiffs filed a Complaint in the district court, alleging that Lupin's ANDA for levofloxacin tablets would infringe the '407 patent and sought a judicial declaration that the term extension granted to the '407

patent under 35 U.S.C. § 156 is valid, and that the '407 patent expires not on its original expiration date of October 1, 2008, but on December 20, 2010, pursuant to the 810-day term extension. *A22, A61-A89 at A69-A70, A1200.*

Lupin's Answer challenged the validity of the patent term extension and sought a judicial declaration that the grant of the term extension to the '407 patent is invalid, and that the marketing of the levofloxacin tablets described in Lupin's ANDA after October 1, 2008 (*i.e.*, after the original expiration date of the '407 patent), would not infringe the '407 patent. *A90-A102 at A101-A102.* Plaintiffs then filed their Reply to Lupin's Counterclaim. *A103-A107.*

On June 11, 2007, the District Court entered a Joint Stipulation and Order relative to the validity, enforceability and infringement of the '407 patent. In pertinent part, Lupin agreed therein that it would not "contest at trial or otherwise the validity or enforceability of the '407 patent or the infringement of claims 2 and 5 of the '407 patent" by the levofloxacin products described in Lupin's ANDA. *A108-A111 at A109, A22.* Further, Lupin agreed that it would "contest at trial only whether the '407 patent is entitled to the term extension granted to it by the PTO pursuant to 35 U.S.C. § 156." *Id.*

The parties subsequently filed cross-motions for summary judgment in which "the sole issue before the Court [was] whether the PTO's extension of the

term of the '407 patent is valid." *A23, A849-A1122, A1123-A2561, A2565-A2820, A2821-A2931, A2562-A2564.*

The district court issued its decision on the cross-motions for summary judgment on April 30, 2009, granting Plaintiffs' motion and denying Lupin's motion and contemporaneously issued an Order enjoining Lupin from various actions. The pertinent part of the district court decision reads as follows:

> In this case, the parties do not dispute that the PTO's prior decision to extend the term of the '407 patent is consistent with the PTO's prior decisions in similar situations. Indeed, following the practice and procedure set out in the MOU [Memorandum of Understanding], the PTO, informed by the expertise of the FDA, has considered at least five other applications for patent term extensions for patents covering enantiomeric products subsequent to approval of their corresponding racemates. In each such case, the PTO and the FDA, acting in concert pursuant to the MOU, have determined that the patent covering the enantiomeric product was entitled to extension, and have granted the patent term extension pursuant to 35 U.S.C. § 156. Thus, the undisputed facts clearly establish the PTO has determined that enantiomers are 'products' eligible for patent term extensions pursuant to 35 U.S.C. § 156, regardless of whether the patent term of the enantiomer's racemate has also been extended. The Federal Circuit's decision in *Quigg* establishes that this Court must give great deference to this determination by the PTO. *Quigg*, 894 F.2d at 399. Having reviewed all of the parties' submissions, the Court concludes that Lupin is not able to present clear and convincing evidence that the PTO's decision to extend the term of the '407 patent is invalid. Because the undisputed evidence reveals that Lupin cannot meet its burden, its motion for summary judgment

> will be denied, and Plaintiffs' motion for summary judgment will be granted.

A26-A27.

On May 5, 2009, Lupin filed a notice of appeal of the district court decision and order. *A15.*

SUMMARY OF ARGUMENT

The primary issue before the Court is whether the term extension that was granted for U.S. Patent No. 5,053,407 ("the '407 patent") is invalid because the extension is contrary to 35 U.S.C. § 156(a)(5)(A). The extension is invalid because levofloxacin, the active ingredient in LEVAQUIN® that formed the basis for the patent term extension, was an active ingredient in the previously-commercialized FLOXIN® product.

Section 156(a) of the Hatch-Waxman Act[1] states that in order to qualify for a patent term extension, the commercial marketing or use of a "product" must be the first permitted (*i.e.,* FDA-approved) commercial marketing or use of the product in the United States. 35 U.S.C. § 156(a)(5). The term "product" is defined in the statute as a "drug product," the latter in turn being defined as an "active ingredient." 35 U.S.C. § 156(f)(1) & (2). The FDA regulations define "active ingredient" as "any component that is intended to furnish pharmacological activity . . . in the diagnosis, cure, mitigation, treatment, or prevention of disease . . . ." 21 C.F.R. § 60.3(b)(2). Accordingly, to qualify for a patent term extension, the patented product must be the first permitted commercial marketing or use in the United States of that active ingredient, *i.e.,* a component that is intended to furnish pharmacological activity in the treatment of disease.

[1] The "Hatch-Waxman Act" is formally known as the "Drug Price Competition and Patent Term Restoration Act of 1984."

The '407 patent claims levofloxacin. There is no dispute that levofloxacin was a component in a commercial product previously approved by the FDA—FLOXIN®. Indeed, levofloxacin was an "active ingredient" in FLOXIN® because it furnished pharmacological activity (as an antimicrobial) in the treatment of disease. Because the approval of LEVAQUIN® was not the first FDA-approved commercial marketing or use of the active ingredient levofloxacin, the grant of the term extension to the '407 patent is invalid.

Of note is the FDA's decision on new product exclusivity for levofloxacin. Before the FDA and the USPTO were asked to decide whether the FDA approval of LEVAQUIN® qualified as the first FDA approval of levofloxacin as an active ingredient in connection with an application for a patent term extension, the FDA decided that levofloxacin was not entitled to a five-year period of new product exclusivity. But qualification for a patent term extension and for a five-year new product exclusivity both hinge on one principal question: Was the approval of the "active ingredient" the first such approval for marketing by the FDA? The FDA did not grant levofloxacin a five-year new product exclusivity, yet did find that the '407 patent claiming levofloxacin was entitled to a patent term extension.

ARGUMENT

I. STANDARD OF REVIEW

A. Appeal From a Summary Judgment Decision

An appellate court must determine whether the strict standard set forth in FED. R. CIV. P. 56(c) has been satisfied. *See Chula Vista City School Dist. v. Bennett,* 824 F.2d 1573, 1579 (Fed. Cir. 1987), *cert. denied,* 484 U.S. 1042 (1988). When both parties concede that there are no genuine issues of material fact, "this Court need only decide the same question of law decided by the district court on summary judgment." *See Glaxo Oper. UK Ltd. v. Quigg,* 894 F.2d 392, 395 (Fed. Cir. 1990). When the issue on appeal concerns statutory interpretation, that issue can be decided by an appellate court ... "without deference to the trial court's interpretation." *See Glaxo,* 894 F.2d at 395 (*citing Madison Galleries, Ltd. v. United States,* 870 F.2d 627, 629 (Fed. Cir. 1989)).

B. Standard of Review Concerning Actions Taken by the USPTO

The USPTO is charged with administering the provisions of 35 U.S.C. § 156 and the underlying rules governing patent term extensions. See 35 U.S.C. § 156(d)(1). In determining the validity of a patent term extension, appropriate deference is to be given to the agency charged with this authority and responsibility. *See Dickinson v. Zurko,* 527 U.S. 150, 152 (1999) (principles of

administrative deference apply to USPTO actions). Any deference owed to a USPTO decision arises not from force of law but rather from "the thoroughness of its consideration and the validity of its reasoning, *i.e.*, its basic power to persuade." *See Merck & Co., Inc. v. Kessler,* 80 F.3d 1543, 1550 (Fed. Cir. 1996) (*citing Skidmore v. Swift & Co.*, 323 U.S. 134, 140 (1944)).

This Court may reverse any USPTO decision if the decision is arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with the law. *See Ray v. Lehman*, 55 F.3d 606, 608 (Fed. Cir. 1995). An abuse of discretion occurs when a decision is based on an erroneous interpretation of the law. *See In re Gartside*, 203 F.3d 1305, 1315-16 (Fed. Cir. 2000). The current appeal is solely concerned with the proper application of uncontested law to uncontested facts. As this Court held in *Glaxo*:

> 'When ... the terms of a statute [are] unambiguous, judicial inquiry is complete, except in rare and exceptional circumstances.' *United States v. James,* 478 U.S. 597, 606 (1986) (quoting *Rubin v. United States,* 449 U.S. 424, 430 (1981) (internal quotation marks omitted)). Moreover, absent a 'clearly expressed legislative intention to the contrary,' a statute's plain meaning 'must originally be regarded as conclusive.' *Consumer Prod. Safety Comm'n v. GTE Sylvania, Inc.,* 447 U.S. 102, 108 (1980).

See Glaxo, 894 F.2d at 392.

II. THE DISTRICT COURT DECISION PROVIDES NO GUIDANCE

The district court's decision can be summarized in one sentence from the opinion: "Thus, the undisputed facts clearly establish the PTO has determined that enantiomers are "products" eligible for patent term extensions pursuant to 35 U.S.C. § 156, regardless of whether the patent term of the enantiomer's racemate has also been extended." *A26.*

From this key statement in the opinion it is apparent that the district court simply gave deference to the practice of the USPTO, based on the advice of the FDA under a Memorandum of Understanding ("MOA"), to deem enantiomers of previously approved racemic mixtures capable of supporting patent term extension. *A19-A20, A26.* In doing so, the district court avoided the real issue in this case: the meaning of the term "active ingredient" and how it should be applied in the present situation. Moreover, the existence or not of a patent term extension related to the racemate is not the issue.

The deference given by the district court to the USPTO's determination, which was based on the July 18, 1997, letter from the FDA, is not warranted. *See Glaxo,* 894 F.2d at 399. That letter from the FDA asserts no special technical expertise, but rather constitutes a complete misinterpretation and misapplication of the relevant case law. Little deference should be accorded to the USPTO or FDA

when the decision of the issue at hand rests not on technical expertise, but rather "on a narrow dissection of statutory language." *See Glaxo,* 894 F.2d at 399.

In pertinent part, the FDA letter to the USPTO that underlies the grant of the '407 patent term extension reads as follows:

> A review of the Food and Drug Administration's official records indicates that this product was subject to a regulatory review period before its commercial marketing or use, as required under 35 U.S.C. § 156(a)(4). Our records also indicate that it represents the first permitted commercial marketing or use of the product, as defined under 35 U.S.C. § 156(f)(1), and interpreted by the courts in *Glaxo Operations UK Ltd. v. Quigg,* 706 F. Supp. 1224 (E.D. Va. 1898), *aff'd*, 894 F. 2d 392 (Fed. Cir. 1990).

A1888.

It is clear that the USPTO relied on the FDA to "make the call" as to whether the approval of FLOXIN® levofloxacin qualified as the first approval of levofloxacin as an *active ingredient* to support a patent term extension. Apparently, the FDA in turn felt constrained by the decision of this Court in *Glaxo* and the underlying district court decision. But this Court's decision in *Glaxo* had nothing to do with enantiomers, and none of the rationale in that decision is even remotely applicable to the undisputed facts presented in this appeal.

As this Court is well aware, at issue in *Glaxo* was the "active ingredient ... including any salt or ester" language in Section 156(f)(2) which reads:

> The term "drug product" means the *active ingredient* of—
>
> (A) a new drug, antibiotic drug, or human biological product (as those terms are used in the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act),
>
> * * *
>
> *including any salt or ester of the active ingredient*, as a single entity or in combination with another active ingredient.

See Glaxo, 894 F.2d at 395 (emphasis added).

There is no such issue in the present appeal. It is undisputed that the molecule levofloxacin was present in the prior-approved FLOXIN® ofloxacin product, and that same molecule is present in the later-approved LEVAQUIN® levofloxacin product. *A17, A1191 (¶ 6), A1192-A1193, A905-A919 at A912-A913.* There is no issue of a prior- or later-approved salt or ester in the present appeal.

III. THE TERM EXTENSION OF THE '407 PATENT IS INVALID FOR FAILING TO SATISFY 35 U.S.C. § 156(a)(5)(A)

A. Not All Newly Approved Drug Products Provide a Basis for a Patent Term Extension

Although Plaintiffs were able to obtain FDA approval to market LEVAQUIN®, Section 156 does not provide for the extension of the patent term for every product that must undergo FDA approval. *See Fisons v. Quigg*, 876 F.2d

99, 101 (Fed. Cir. 1989). The requirements for obtaining a patent term extension differ from those pertaining to patentability; the USPTO often grants patents on different polymorphic forms of drugs, controlled release dosage forms of drugs and combinations of drugs—and the FDA grants approvals for such products—but not all of these are entitled to patent term extensions. *See, e.g., Arnold Partnership v. Dudas*, 362 F.3d 1338, 1341-43 (Fed. Cir. 2004).

Lupin does not dispute that the patent term extension granted to the '407 patent satisfies 35 U.S.C. § 156(a)(1)-(4). What is disputed, however, is whether the fifth requirement of Section 156(a) is satisfied, specifically, whether the approval of LEVAQUIN® (levofloxacin drug product) represents the "first permitted commercial marketing or use of the product" when the term "product" is properly construed. 35 U.S.C. § 156(a)(5). The USPTO, based on legal advice from the FDA, improperly applied the term "product," finding that levofloxacin was not an "active ingredient" in a prior drug approved by the FDA. The USPTO action in granting the patent term extension for the '407 patent was arbitrary and capricious or otherwise not in accordance with the law. When Section 156 is properly construed and applied to the undisputed facts, it is clear that the patent term extension granted to the '407 patent is invalid.

B. The Term "Product" Means an Active Ingredient of a Drug Either Alone or in Combination with Another Active Ingredient

Statutory construction requires an initial examination of the statute, and interpreting the words of the statute in accordance with their ordinary, common meaning unless otherwise defined by Congress. *See, e.g., Hoechst-Roussel Pharm., Inc. v. Lehman,* 109 F.3d 756, 758 (Fed. Cir. 1997). "It is well settled law that the plain and unambiguous meaning of the words used by Congress prevails in the absence of a clearly expressed legislative intent to the contrary." *See Hoechst Aktiengesellschaft v. Quigg*, 917 F.2d 522, 526 (Fed. Cir. 1990).

The statutory requirements under 35 U.S.C. § 156 for grant of a patent term extension state in relevant part:

> (a) The term of a patent which claims a product, a method of using a product, or a method of manufacturing a product shall be extended in accordance with this section from the original expiration date of the patent, which shall include any patent term adjustment granted under section 154(b), if—
>
> (5)(A) except as provided in subparagraph (B) or (C), the permission for the commercial marketing or use of the product after such regulatory review period is the first permitted commercial marketing or use of the product under the provision of law under which such regulatory review period occurred;
>
> * * *

(f) For purposes of this section:

(1) The term "**product**" means:

(A) A drug product.

* * *

(2) The term "**drug product**" means the **active ingredient** of—

(A) a new drug, antibiotic drug, or human biological product (as those terms are used in the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act), or

* * *

including any salt or ester of the active ingredient, **as a single entity or in combination with another active ingredient.**

35 U.S.C. § 156 (emphasis added).

Section 156(f) defines the term "product" as a "drug product," which is further defined in the statute as an "active ingredient of a new drug . . . including any salt or ester of the active ingredient, *as a single entity or in combination with another active ingredient*." 35 U.S.C. § 156(f)(2) (emphasis added).

This Court has already agreed with Lupin's position, interpreting the meaning of the term "product" in Section 156(a)(5)(A) to be defined by Section 156(f) to mean the drug's "active ingredient." *See Fisons*, 876 F.2d at 100, 102. Substituting the statutorily-prescribed definition of "product" into the fifth subsection of Section 156(a) yields the following:

> (a) The term of a patent which claims **[an active ingredient . . . as a single entity or in combination with another active ingredient]** . . . shall be extended in accordance with this section from the original expiration date of the patent . . . if—
>
> * * *
>
> (5)(A) . . . the permission for the commercial marketing or use of the **[active ingredient . . . as a single entity or in combination with another active ingredient]** after such regulatory review period is the first permitted commercial marketing or use of the **[active ingredient . . . as a single entity or in combination with another active ingredient]** under the provision of law under which such regulatory review period occurred . . . .

35 U.S.C. § 156 (emphasis added).

Thus, if the '407 patent claims an active ingredient (as a single entity or in combination with another active ingredient), the '407 patent term can only be extended if the permission for the commercial marketing [*i.e.*, FDA approval] is the first such permitted commercial marketing or use of the active ingredient as a single entity or in combination with another active ingredient.

There is no factual dispute that the '407 patent claims levofloxacin. There also is no dispute that levofloxacin was a component of a product (FLOXIN®), as an enantiomer in the ofloxacin racemate), which product (FLOXIN®) was approved for marketing by the FDA well prior to the approval and marketing of Plaintiffs' levofloxacin product (LEVAQUIN®).

Thus, the fifth requirement for a patent term extension would not be met if levofloxacin, when present as part of the racemate in FLOXIN®, is an "active ingredient" under Section 156. In other words, the FDA approval for marketing LEVAQUIN® would not be the "first permitted commercial marketing or use" of the active ingredient (levofloxacin) as either a single entity or in combination with another active ingredient, and such prior approval cannot support a patent term extension under Section 156.

C. This Court Has Declared the Term "Active Ingredient" to be "Well-Defined"

This Court has previously analyzed Section 156, and specifically the term "active ingredient" and concluded that the term "had [a] well-defined, ordinary, common meaning[s] when Congress enacted the [Hatch-Waxman] Act [in 1984]." *See Glaxo,* 894 F.2d at 395.

The definition of the term "active ingredient" adopted by the FDA in the 1970s has remained unchanged to date—despite changes to the Hatch-Waxman Act since its enactment in 1984. *A885-A887 (¶ 12), A1088-A1098.* The term "active ingredient" means "any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man of or animals." *Id.;* 21 C.F.R. § 210.3(b)(7). This same definition

was specifically incorporated into the FDA regulations concerning patent term extensions when those regulations were first issued in 1988. The definition of "active ingredient" in the patent term extension regulations has also remained unchanged to date; it is the same as the definition set forth in 21 C.F.R. § 210.3(b)(7). *A1092-A1098.* Indeed, this was the definition of active ingredient at the time Plaintiffs applied for an extension of the '407 patent term, and was the very same definition referenced by this court when it analyzed the meaning of Section 156. *See, e.g., Merck & Co., Inc. v. Teva Pharms. USA, Inc.*, 347 F.3d 1367, 1373 (Fed. Cir. 2003).

It is undisputed that the levofloxacin in FLOXIN® provided pharmacological activity, and is thus an "active ingredient" under Section 156. For example, the '407 patent asserts that levofloxacin exhibits stronger antimicrobial activity than does the R(+)-enantiomer of ofloxacin, but that the R(+)-enantiomer exhibits antimicrobial activity nonetheless. *A31.* In addition to the activity described in the '407 patent, a district court opinion in a prior levofloxacin case brought by the Plaintiffs confirms the existence of the pharmacological activity of ofloxacin and its enantiomers, primarily the S(-)-enantiomer of ofloxacin. *See Ortho-McNeil*, 348 F. Supp. 2d at 751, *A1193.* Indeed, the district court in the present action specifically found that "[i]n previous litigation, Plaintiffs

acknowledged that ... Levofloxacin is one of two biologically active enantiomers present in Ofloxacin." *A17, A1193 (¶ 12).*

Thus, the FLOXIN® ofloxacin product included levofloxacin as an active ingredient, either alone or in combination with the R(+)-enantiomer of ofloxacin. Because levofloxacin is an "active ingredient" as that term is properly defined (21 C.F.R. § 210.3(b)(7)), the term extension granted to the '407 patent is invalid since "a patent is ineligible for extension if it is not the first permitted commercial marketing or use of the active ingredient contained in that approved patented product." *See Fisons,* 876 F.2d at 100 (*citing Fisons PLC v. Quigg,* 1988 WL 150851 *1, *5 (D.D.C. Aug. 19, 1988)).

Further, since Section 156 defines the term "product" to mean "the active ingredient . . . as a single entity or in combination with another active ingredient," the statute clearly prohibits a patent term extension when the basis for the extension is an active ingredient (levofloxacin) that was present in an earlier FDA-approved dosage form as an active ingredient, even if it was present in combination with another active ingredient (e.g., the R(+)-enantiomer of ofloxacin). *See Arnold Partnership,* 362 F.3d at 1341.

IV. THE TERM "ACTIVE INGREDIENT" MUST MEAN THE SAME IN THE PATENT TERM EXTENSION PROVISIONS OF 35 U.S.C. § 156 AND IN THE NEW PRODUCT EXCLUSIVITY PROVISIONS OF 21 U.S.C. § 355

A. This Court Has Acknowledged the Required Nexus Between the Section 156 Patent Term Extension Provisions of the Hatch-Waxman Act and the New Product Exclusivity Provisions of That Same Act

The Hatch-Waxman Act comprises Title I, which concern various FDA-related issues relating to the approval of "generic" drugs, and Title II, which relates to patent term extensions, the latter restoring part of the life of a patent based on the delay that is encountered in obtaining FDA approval for drugs that contain new active ingredients. The patent term provisions of 35 U.S.C. § 156 were part of Title II of the Hatch-Waxman Act of 1984. *See Merck & Co.*, 80 F.3d at 1543-44. The Hatch-Waxman Act new product exclusivity provisions are now codified, *inter alia*, as 21 U.S.C. §§ 355(c)(3)(E)(ii) and 355(j)(5)(F)(ii). These provisions provide for the grant of five years of exclusivity to new FDA regulated drugs provided that "no active ingredient" of that drug has been previously approved by the FDA. The FDA has promulgated regulations that are directed to this five-year exclusivity period, including 21 C.F.R. § 314.108:

§ 314.108 New drug product exclusivity

(a) *Definitions.* The following definitions of terms apply to this section:

Active moiety means the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance.

This Court in *Pfizer, Inc. v. Dr. Reddy's Labs., Ltd.*, 359 F.3d 1361, 1366 (Fed. Cir. 2004), *while deciding the meaning of the term "active ingredient" in the context of determining the proper scope of a patent term extension under Section 156(f),* turned to the above-quoted FDA regulation that relates to the five year Hatch-Waxman exclusivity period for "new" active ingredients:

> As we observed, 35 U.S.C. § 156(f) defines the drug product as including 'any salt or ester of the active ingredient.' *See Abbott Laboratories, Inc. v. Young,* 920 F.2d 984, 985-89 (D.C. Cir. 1990). The FDA ruled that 'the term 'active ingredient' as used in the phrase 'active ingredient including any salt or ester of the active ingredient' means active moiety.' *Abbreviated New Drug Application Regulations: Patent and Exclusivity Provisions,* 59 Fed. Reg. 50,338, 50,358 (F.D.A. Oct. 3, 1994). The FDA has defined 'active moiety' as 'the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt ... responsible for the physiological or pharmacological action of the drug substance.' 21 C.F.R. § 314.108(a).

Hence, this Court has specifically relied upon the FDA'a regulations relating to *new product exclusivities* to construe the same term "active ingredient" as used in the *patent term extension* provisions of Section 156(f)(2). This approach was not only proper, it is required. When identical words appear in different parts of the same Congressional Act, those words should be construed to have the same meaning. *See Voracek v. Nicholson*, 421 F.3d 1299, 1304 (Fed. Cir. 2005) ("identical words used in different parts of the same act are intended to have the same meaning" under the "normal rule of statutory construction") (*citing Gustafson v. Alloyd Co.*, 513 U.S. 561, 570 (1995), *quoting Dep't of Revenue of Or. v. ACF Indus., Inc.*, 510 U.S. 332, 342 (1994)).

Accordingly, this Court has recognized that the term "active ingredient" must mean the same in both the Section 156 patent term extension provisions and in the new product exclusivity provisions. Levofloxacin qualifies as a newly approved "active ingredient" in neither.

Levofloxacin did not qualify for the five year ("NCE") because LEVAQUIN® did not represent the first FDA approval of levofloxacin as an "active ingredient." According to the FDA, enantiomers, such as the levofloxacin active ingredient in LEVAQUIN®, do not qualify for such exclusivity if the corresponding racemic mixture containing that enantiomer was previously approved as a drug. A decade ago the FDA formalized its position that a single

enantiomer of a previously approved racemate is not considered a "new" active ingredient. *See* 54 Fed. Reg. 28872 at 28898 (July 10, 1989). For that same reason such enantiomers do not qualify for patent term extensions. Hence, although FLOXIN®, which contains the two enantiomers, *i.e.*, levofloxacin and the corresponding R(+)-enantiomer, was given five-year new product exclusivity, LEVAQUIN® was not. *A2645 (¶¶ 11 and 12), A2789-A2790, A2791-A2792.*

B. Congress Has Interpreted the Term "Active Ingredient" As Used in the New Product Exclusivity Provisions in the Same Manner as the FDA

The FDA has always denied awarding five-year regulatory exclusivity for an enantiomer when that enantiomer had been previously approved by the FDA as part of a racemic mixture. Congress, through legislation enacted in 2007 (Pub. L. No. 110-85), for the first time created a special amendment to the new product exclusivity provisions to provide a previously-approved enantiomer with such new product exclusivity, but only under very stringent conditions, which, *inter alia*, require an election by the NDA applicant to be given the benefit of such special conditions. Most notably, in this new legislation *Congress addressed the meaning of the term "active ingredient" in the specific exclusivity provisions discussed previously and specifically in the context of enantiomers.* The language used by Congress in the legislation is quoted below, but for the sake of application to the

facts of the present appeal, the terms ofloxacin and levofloxacin have been included in brackets:

> For purposes of subsections (c)(3)(E)(ii) and (j)(5)(F)(ii), if an application is submitted under subsection (b) for a non-racemic drug containing as an active ingredient (including any ester or salt of the active ingredient) a single enantiomer [levofloxacin] that is contained in a racemic drug [ofloxacin] approved in another application under subsection (b), the applicant may, in the application for such non-racemic drug [levofloxacin], elect to have the single enantiomer [levofloxacin] **not be considered the same active ingredient as that contained in the approved racemic drug.**

A2643-A2646 (¶ 13), A2793-A2799 at A2797 (emphasis added).

It could not be more clear that Congress interpreted the term "active ingredient" as used in the new product exclusivity provisions exactly as used by Lupin. This new legislation is directly on point because it addresses the meaning of the term "active ingredient" in the context of enantiomers. Absent this special election by an NDA applicant under this new legislation, an enantiomer of a prior approved racemic mixture *would continue to be considered* to be "the same active ingredient as that contained in the approved racemic drug," this being the position taken by the FDA for two decades.

Although this new legislation is directed to new product regulatory exclusivities and not patent term extensions, the issue is still the same – the meaning of the term "active ingredient" in the context of enantiomers as arising in

the present appeal. As clearly recognized by Congress, an enantiomer in a non-racemic drug such as LEVAQUIN® is the same "active ingredient" as that contained in the prior approved racemic drug. There is no special definition of "active ingredient" that applies to one part of the Hatch-Waxman legislation when dealing with regulatory exclusivity and another definition that applies when dealing with patent term extensions. The precedent of this Court and that of the U.S. Supreme Court requires that "identical words used in different parts of the same act are intended to have the same meaning" under the "normal rule of statutory construction." *See Dep't of Revenue of Or.*, 510 U.S. at 342.

The extension of the patent term for the '407 patent was arbitrary and capricious and/or contrary to law, and the decision of the district court upholding the validity of this term extension should be reversed.

V. THE SCOPE OF THE INJUNCTION IS OVERLY BROAD

A. Description of the Injunction As Granted

The district court granted an injunction whereby Lupin is enjoined from making, using, offering to sell, selling or importing the levofloxacin tablets described in ANDA No. 78-424 or bulk levofloxacin for use in manufacturing such tablets.

B. The Rights Granted Under 35 U.S.C. § 156 Are Limited to FDA Approved Uses

The '407 patent has expired, except for the rights that are granted pursuant to Section 156(b), which as noted by this Court in *Pfizer*, are specifically limited to "any use approved for the product." *See Pfizer, Inc. v. Dr. Reddy's Labs., Ltd.*, 359 F.3d 1361, 1366 (Fed. Cir. 2004). In the present context "approved" must mean any drug use approved by the FDA. The FDA approved uses for levofloxacin all relate to its use as an antimicrobial agent for the treatment of humans in the United States. *A885-A887 (¶ 9), A1051-A1059 at A1054.*

C. The Injunction Exceeds the Scope Authorized By 35 U.S.C. § 156

The district court's injunction was improper and contrary to law as the limited rights provided by Section 156 do not provide authority to enjoin Lupin from making or importing levofloxacin tablets or from making or importing bulk levofloxacin. The injunction accordingly should be modified if Lupin does not prevail with respect to its appeal challenging the validity of the patent term extension that was granted to the '407 patent.

CONCLUSION

Lupin respectfully requests that this Court reverse the judgment of the district court that the patent term extension granted to U.S. Patent No. 5,053,407 is valid, and reverse the district court's order granting injunctive relief.

Respectfully submitted,

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