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 FOR THE UNITED STATES AS AMICUS CURIAE IN SUPPORT OF THE APPELLEES

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Statement of Related Cases

In a prior appeal, this Court affirmed the district court's construction of the claims of U.S. Patent No. 5,053,407 (the "'407 patent") and upheld the validity of the '407 patent. See *Ortho-McNeil Pharm. Inc. v. Mylan Labs., Inc.*, 161 Fed. Appx. 944 (Fed. Cir. 2005). As far as we know, no other appeal in or from the present civil action has previously been before this or any other appellate court. Counsel is aware of the following related case currently pending before this Court: *PhotoCure ASA v. Doll*, No. 2009-1393. The sole issue in *PhotoCure* is the meaning of the term "active ingredient" in 35 U.S.C. 156(f), which is one of the issues involved in the instant case. *PhotoCure*, which is still being briefed, has not yet been scheduled for oral argument.

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STATEMENT OF INTEREST

Pursuant to 28 U.S.C. 517 and Rule 29(a) of the Federal Rules of Appellate Procedure, the United States submits this brief as amicus curiae to address the meaning of the term "active ingredient" in the patent term extension provisions of the Hatch-Waxman Act, 35 U.S.C. 156. As the Court is aware, the United States

Patent and Trademark Office (USPTO) is charged with administering the patent term extension provisions of the Hatch-Waxman Act, see *Pfizer, Inc. v. Ranbaxy Labs Ltd.*, 457 F.3d 1284, 1290 (Fed. Cir. 2006); *Merck & Co., Inc. v. Teva Pharmaceuticals USA, Inc.*, 347 F.3d 1367, 1373 (Fed. Cir. 2003), and therefore has a strong interest in making the Court aware of its position on this statutory question.

Although this case involves a private patent infringement suit, at the heart of the case is a decision of the USPTO to extend the term of a patent based on the agency's determination under 35 U.S.C. 156 that the "active ingredient" in the approved drug product had not previously been approved for marketing by the Food and Drug Administration (FDA). USPTO interprets "active ingredient" in Section 156 to mean the active moiety of a drug, and in *Pfizer Inc. v. Dr. Reddy's Laboratories, Ltd.*, 359 F.3d 1361 (Fed. Cir. 2004), this Court adopted the same interpretation. Applying the definition that the *Pfizer* Court ultimately adopted, the USPTO granted an extension of the patent at issue. Thus, like the appellees, the United States believes that the district court's judgment should be affirmed.

The meaning of "active ingredient" in Section 156 is also presented in the government's appeal in *PhotoCure ASA v. Doll*, 2009-1393 (Fed. Cir.), which is currently in the briefing stage. *PhotoCure* is a suit against the USPTO that

directly challenges the agency's interpretation of "active ingredient." Unlike the district court in this case, the district court in *PhotoCure* squarely addressed the "active ingredient" issue. See *PhotoCure ASA v. Dudas*, ___ F. Supp.2d ___, 2009 WL 855807 (E.D.Va. March 31, 2009) at *3-*9 (A2940-48). Moreover, it is not possible to resolve *PhotoCure* without addressing the meaning of "active ingredient," whereas the district court's decision and the parties' briefing suggest that this appeal can be resolved without addressing that issue. For these reasons, the government regards *PhotoCure* as a better vehicle for addressing the meaning of "active ingredient." Nevertheless, to the extent that the Court may choose to address that issue here, the United States is appearing as an amicus to present the USPTO's views on the issue.[1]

STATEMENT OF ISSUE

Whether the "active ingredient" of a drug as that term is used in 35 U.S.C. 156 is the drug's "active moiety" — *i.e.*, the portion of the molecule that gives the drug its therapeutic effect — as this Court held in *Pfizer Inc. v. Dr. Reddy's Laboratories, Ltd.*, 359 F.3d 1361 (Fed. Cir. 2004).

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[1] On July 10, 2009, the United States filed a motion requesting the Court to expedite *Photocure* so that the two appeals may be argued at the same time before the same panel.

STATEMENT OF THE CASE

A. Section 156(b) Patent Term Extensions.[2]

At issue in this case are provisions of the Drug Price Competition and Patent Term Restoration Act of 1984, known as the Hatch-Waxman Act. Pub. L. No. 98-417, 98 Stat. 1585 (1984), *codified at* 21 U.S.C. 355, 360cc, and 35 U.S.C. 156, 271, 282. The Hatch-Waxman Act has dual goals: (1) increasing the number of lower-cost generic drugs on the market and (2) preserving the incentive for manufacturers to perform the research and development necessary to create new pioneer drugs. See H.R. Rep. No. 857 (Part I), 98th Cong., 2d Sess. at 14-15 (1984), *reprinted in* 1984 U.S.C.C.A.N. at 2647. See also *Pfizer Inc. v. Dr. Reddy's Laboratories, Ltd.*, 359 F.3d 1361 (Fed. Cir. 2004).

Title I of the Act was intended "to make available more low cost generic drugs by establishing a generic drug approval procedure for pioneer drugs first approved after 1962." 1984 U.S.C.C.A.N. at 2647. Title II was intended to provide a new incentive for research and development of pioneer drugs by providing "restoration of some of the time lost on patent life while the product is awaiting pre-market approval." *Id.* at 2648. See also, *e.g.*, *Fisons v. Quigg*, 1988 WL 150851, at *3 (D.D.C. Aug. 19, 1988) (Congress recognized "that the

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[2] The pertinent statutory provisions are attached as Addendum A to this brief.

effective market lives" of certain patented inventions — particularly, pharmaceutical products — "were being eroded by excessively long periods of regulatory review by the Food and Drug Administration"), *aff'd*, 876 F.2d 99 (Fed. Cir. 1989). The statutory scheme crafted by Congress represents a delicate balancing of these two policy goals. See *Pfizer Inc. v. Dr. Reddy's Laboratories, Ltd.*, 359 F.3d at 1364-65; *Tri-Bio Labs, Inc. v. United States*, 836 F.2d 135, 139 (3d Cir. 1987), *cert. denied*, 488 U.S. 818 (1988). See also *Eli Lilly and Co. v. Medtronic, Inc.*, 496 U.S. 661 (1990).

This case involves the patent term extension provisions of Title II, codified in 35 U.S.C. 156. Generally, a United States patent has a term of twenty (20) years, running "from the date on which the application for the patent was filed in the United States." 35 U.S.C. 154(a)(2). However, 35 U.S.C. 156 provides extensions for the terms of certain drugs. The term of a drug patent qualifies for an extension where, in pertinent part, the patent "claims a product" (subsection (a)) that "has been subject to a regulatory review period before its commercial marketing or use" (subsection (a)(4)), and "the permission for the commercial marketing or use * * * after [the] regulatory review period is the first permitted commercial marketing or use of the product [under the statutory scheme establishing the regulatory review period]" (subsection (a)(5)). In short, the

FDA's approval of the drug product supporting the patent term extension application must represent the first FDA approval of the "product," as that term is defined in the statute.

B. The USPTO's Interpretation of "Active Ingredient" in Section 156.

Because a drug is not eligible for a patent term extension if the "product" has previously been approved for marketing by the FDA, the meaning of "product" is critical to the scope and operation of the patent term extension provision. Section 156(f)(1)(A) defines "product" to mean "drug product." In turn, Section 156(f)(2) provides that "drug product" means "the *active ingredient* * * * of a new drug, * * * including *any salt or ester of the active ingredient* * * * * " (emphasis added). Thus, eligibility for a patent term extension turns on whether the "active ingredient" of the current drug, *including* "any salt or ester" of the active ingredient, has previously been approved by the FDA.

The Hatch-Waxman Act does not define "active ingredient." However, the USPTO has construed the term administratively in the course of administering the patent term extension provisions of the Hatch-Waxman Act. USPTO interprets "active ingredient" — consistent with the holding in *Pfizer*, *supra* — to be a synonym for "active moiety." Generally speaking, the active moiety of a drug is

the portion of the drug that produces the pharmacological effect. The FDA, as *Pfizer* noted, has defined "active moiety" more specifically as "the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester [or] salt * * *, responsible for the physiological or pharmacological action of the drug substance," 359 F.3d at 1366, quoting 21 C.F.R. 314.108(a), and the USPTO relies on the same definition.[3] Thus, if the active moiety of the drug product for which an application for a patent term extension has been filed is *not* the same active moiety in a drug product previously approved by the FDA, the USPTO will (as it did here) grant the application.

STATEMENT OF FACTS

1. Factual background.

In 1983, the USPTO issued U.S. Patent 4,382,892 (the "'892 patent") to Daiichi. The '892 patent claims ofloxacin, an antimicrobial agent. In 1990, the FDA approved ofloxacin tablets for commercial marketing, and the tablets were subsequently marketed under the trademark Floxin®. The FDA-approved labeling and FDA's Orange Book entry for Floxin® say the "active ingredient" is "ofloxacin."

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[3] USPTO has not promulgated any formal regulation regarding the meaning of "active ingredient."

Ofloxacin contains two enantiomers. Enantiomers are compounds that contain the same elements and the same chemical bonds, but are complete mirror images of each other (and are distinguished through their optical activity or the direction in which the enantiomers rotate a plane of polarized light). The combination of both enantiomers in equal parts forms what is called the racemate of the constituent enantiomers. In previous litigation, *Ortho-McNeil Pharmaceutical, Inc. v. Mylan Labs., Inc.*, 348 F. Supp.2d 713 (N.D. W. Va. 2004), *aff'd*, 161 Fed. Appx. 944 (Fed. Cir. 2005), Ortho-McNeil acknowledged that: (1) levofloxacin is one of two biologically active enantiomers present in ofloxacin; and (2) levofloxacin and its corresponding enantiomer are present in ofloxacin in a 1:1 ratio. A17-18.

In 1985, Daiichi scientists succeeded in synthesizing levofloxacin, using novel synthesis routes because it was unable (after years of trying) to obtain it directly from racemic ofloxacin by separating the two enantiomers. Levofloxacin, the levorotatory[4] enantiomer of ofloxacin that the Daiichi scientists synthesized in 1985, is substantially optically pure and is approximately twice as active as racemic ofloxacin — the maximum possible difference in activity between an

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[4] "Levo" refers to the left-hand enantiomer; "dextro" would refer to the right-hand. Levofloxacin is referred to as the S(-)-enantiomer in ofloxacin; its mirror image counterpart is referred to as the R(+)-enantiomer.

enantiomer and its racemate. In addition, levofloxacin is less toxic and ten times more water-soluble than ofloxacin. A18.

In June 1986, Daiichi filed a patent application for levofloxacin, which was ultimately granted by the USPTO as U.S. Patent No. 5,053,407 (the "'407 patent") issued on October 1, 1991. In December 1996, the FDA granted marketing approval for injectable and tablet formulations of levofloxacin as patented in the '407 patent. Levofloxacin has been marketed under the trademark Levaquin®, and FDA's approved labeling and Orange Book entry for Levaquin® say the "active ingredient" is "levofloxacin." A18-19.

In February 1997, Daiichi submitted a timely application for extension of the '407 patent term pursuant to 35 U.S.C. 156. In its transmission to the FDA, the USPTO indicated that the '407 patent, "would be eligible for extension of the patent term under 35 U.S.C. § 156 if the approval of LEVAQUIN is the first permitted marketing or use of the active ingredient thereof," and that, "[Daiichi] has stated that the 'corresponding racemate Floxin' has been previously approved." FDA responded that "[a] review of [its] official records indicates that [Levaquin®] was subject to a regulatory review period before its commercial marketing or use" and "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. 1989), *aff'd*, 894 F.2d 392 (Fed. Cir. 1990)." In August 1999, the USPTO granted an extension of 810 days, from October 1, 2008, to December 20, 2010. A19-21.

2. The district court proceedings.

The instant litigation arises out of the 2006 submission of an abbreviated new drug application (ANDA) filed by Lupin Pharmaceutical, Inc. and Lupin Ltd. (collectively "Lupin") pursuant to 21 U.S.C. 355(j) to market a generic copy of Levaquin®, beginning on October 1, 2008. The October 2008 date, according to Lupin's ANDA, is the date the '407 patent expired. As required by statute, Lupin notified Ortho-McNeil Pharmaceutical, Inc., *et al.* (collectively "Ortho-McNeil"[5]) of the ANDA filing, and Ortho-McNeil responded with a patent infringement suit pursuant to 35 U.S.C. 271(e). Ortho-McNeil asserted that the patent term had been extended by USPTO to December 20, 2010, and that marketing prior to that date would infringe the patent. Lupin countered that the patent term extension was improperly granted. A21-22.

Both parties filed motions for summary judgment, agreeing that there were no disputed facts and that the sole issue was whether levofloxacin, the active

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[5] Ortho-McNeil is an exclusive licensee of the '407 patent from Daiichi. See Ortho-McNeil Br. at 5.

ingredient in Levaquin®, was also the "active ingredient" (or one of the active ingredients) in ofloxacin (Floxin®), which the FDA had approved prior to approving Levaquin®. If so, as Lupin maintained, the patent term extension was erroneously granted, freeing Lupin to market its generic drug commencing on October 1, 2008, provided the FDA approved its ANDA. A22-23.

Lupin's principal argument was that levofloxacin is also present in racemic ofloxacin as an active ingredient. Lupin relied on FDA regulations defining "active ingredient" for good manufacturing and patent term extension purposes. See A867-68 (quoting 21 C.F.R. 210.3(b)(7) ("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 many or of animals")).[6] See also A2572-73 (quoting 21 C.F.R. 210.3(b)(7) & 21 C.F.R. 60.3(b)(2)). Applying the definition, Lupin argued that the active ingredient in levofloxacin is the S(-)-enantiomer of ofloxacin (which is levofloxacin) and the active ingredient in the earlier-approved ofloxacin is also the S(-)-enantiomer because the S(-)-enantiomer

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[6] Lupin also cited *Glaxo Operations UK Ltd. v. Quigg*, 894 F.2d 392 (Fed. Cir. 1990), for the proposition that the term "active ingredient" had a well-defined meaning when the Hatch-Waxman Act was enacted. See A867.

is a component of the racemate ofloxacin and imparts pharmacological activity. See A869-70.

Ortho-McNeil argued *Glaxo*, not *Pfizer*, defines "active ingredient" and, like Lupin, relied on the definition of "active ingredient" in the same FDA regulations. See A1142-43 & n.6 & A1158 (citing 21 C.F.R. 60.3(b)(2) and C.F.R. 210.3(b)(7)).[7] Ortho-McNeil disagreed with Lupin, however, on the application of that definition to the facts. See A1143 ("the issue presented by these dueling motions is not one of statutory interpretation, but rather the application of the longstanding definition of 'active ingredient' by the FDA when it approved the racemic product"). It asserted that the component furnishing pharmacological activity in the earlier-approved ofloxacin is the racemate as a whole — the R(+)- and S(-)-enantiomers as an indivisible unit, rather than just the S(-)-enantiomer. A1157-64.

Ortho-McNeil also argued that USPTO had previously extended the terms of patents in five identical situations and that, under *Glaxo*, 894 F.2d at 399, the USPTO is entitled to great deference in determining which active ingredients are

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[7] Ortho-McNeil argued that *Pfizer* was inapplicable because it concerned the scope of a patent holder's rights during the extension period as defined by 35 U.S.C. 156(b), not eligibility for such an extension under Section 156(a), and that *Pfizer* could not have overruled the earlier *Glaxo* decision. See A1142 n.6.

entitled to patent term extension. A1151-56. Thus, Ortho-McNeil argued, Lupin's burden was to produce clear and convincing evidence that the USPTO acted arbitrarily and capriciously in treating levofloxacin the same way it treated the five previous identical situations, which Lupin failed to do. A1128, A1138-45, A1140 n.4, A1151-56, and A1167.

The district court upheld USPTO's patent term extension based solely on Ortho-McNeil's second argument referenced above. The court did not address the meaning of the term "active ingredient" or any other term in Section 156. A26-27.

SUMMARY OF THE ARGUMENT

1. To the extent this Court is required to address the meaning of "active ingredient" in 35 U.S.C. 156 to resolve this appeal, the Court's decision in *Pfizer Inc. v. Dr. Reddy's Laboratories, Ltd.*, 359 F.3d 1361, is the governing precedent. *Pfizer* squarely addressed the meaning of "active ingredient" and defined it to mean "active moiety." Ortho-McNeil argues that *Glaxo Operations UK Limited v. Quigg*, 894 F.2d 392, governs, but as we demonstrate below, it is clear that *Glaxo* had no occasion to address the meaning of "active ingredient" and did not do so. In employing the same "active moiety" interpretation later endorsed in *Pfizer*, the USPTO granted Ortho-McNeil's patent term extension application. Under *Pfizer*,

that determination — for which the USPTO is entitled to great deference — must be sustained.

2. Even if *Pfizer* were not controlling, the USPTO's interpretation of the "active ingredient" in 35 U.S.C. 156 is persuasive and should be upheld. 35 U.S.C. 156(f)(2)(A) defines "drug product" to mean (in pertinent part) "the active ingredient of * * * a new drug, * * * including any salt or ester of the active ingredient," but it does not define "active ingredient." USPTO reads the definition of "drug product" to encompass three categories of molecules: (1) the non-salified and non-esterified form of a molecule, (2) any salt of that molecule; and (3) any ester of that molecule. Parsing the language, the USPTO interprets "active ingredient" to refer to the first category of molecule, which is the active moiety — the pharmacologically active molecule to which components are added to make it a salt or ester. In *Pfizer*, the Court reasoned similarly, reading the reference to "any salt or ester of the active ingredient" as an indication that Congress did not conceive of individual salts and esters as themselves constituting distinct active ingredients for patent term extension purposes.

If "active ingredient" is understood to mean active moiety, it is entirely coherent to speak of salts and esters of the active moiety. Such a reading also makes sense of the "including" clause, inasmuch as the "active ingredient" is the

component before "including" other components that make it a salt or ester. As added support for the USPTO's interpretation, it is significant that the FDA, which is faced with virtually identical statutory language in administering the market exclusivity provisions of Title I of the Hatch-Waxman Act, has adopted the same reading that the USPTO employs here. Furthermore, both the legislative history and public policy support the USPTO's position.

ARGUMENT

FOR PURPOSES OF PATENT TERM EXTENSION UNDER 35 U.S.C. 156, THE "ACTIVE INGREDIENT" OF A DRUG IS THE DRUG'S ACTIVE MOIETY.

The ultimate issue in this appeal is whether ofloxacin, a racemate, and levofloxacin, one of the two enantiomers that make up the racemate, constitute the same "active ingredient" (and hence the same "product") for purposes of the patent term extension provisions of 35 U.S.C. 156. In the course of addressing that question, however, the parties have raised a legal question of considerably broader import — the meaning of "active ingredient" under Section 156.

Appearing to rely on this Court's decision in *Pfizer*, which relies in turn on the FDA's interpretation of "active ingredient" under the marketing exclusivity provisions of the Hatch-Waxman Act, Lupin seems to argue that the "active ingredient" of a drug is the drug's active moiety. Lupin Br. at 29-30. Ortho-

McNeil, in contrast, dismisses *Pfizer* and the FDA's marketing exclusivity regulations as inapposite and argues that the Court's earlier decision in *Glaxo* holds that "active ingredient" in Section 156 does *not* mean active moiety. Ortho-McNeil Br. at 32-36.

Ortho-McNeil, however, also notes that applying *Pfizer*'s "active moiety" approach does not preclude treating ofloxacin and levofloxacin as different active ingredients. *Id.* at 38-39. As a result, this Court ultimately may be able to resolve this appeal without having to address the parties' disagreement about the meaning of "active ingredient" and the relevance of *Pfizer* and *Glaxo*. But to the extent that the Court does find itself addressing that dispute, the United States wishes to be heard as an *amicus* on the issue, for the meaning of "active ingredient" under the patent term extension provisions of the Hatch-Waxman Act has significance outside the confines of this case and beyond the specific context of racemates and enantiomers.

A. *Pfizer* Establishes that "Active Ingredient" Means "Active Moiety," which is the Meaning the USPTO Applied in This Case.

1. The meaning of "active ingredient" under Section 156 is not an issue of first impression in this Court. In *Pfizer*, this Court held squarely that "active

ingredient" in Section 156 means "active moiety." See 359 F.3d at 1365-66. That holding governs this appeal.

Pfizer involved a patent term extension on a patent protecting the drug Norvasc, which has the chemical name amlodipine besylate. Amlodipine besylate is a salt of the active moiety amlodipine. Dr. Reddy's sought to market amlodipine maleate, a different salt of the same active moiety. Pfizer sued Dr. Reddy's for infringement, and Dr. Reddy's defended by arguing that the patent term extension was limited to the particular salt approved by the FDA, amlodipine besylate. Pfizer, in contrast, argued that its patent term extension covered amlodipine and all of its salt forms. This Court agreed with Pfizer, holding that "the active ingredient is amlodipine" — the active moiety of both drugs — and that "[t]he statutory definition of 'drug product' is met by amlodipine and its salts." 359 F.3d at 1366.

Parsing the statutory language, *Pfizer* reasoned that, by "defining the term 'product' as 'including any salt or ester of the active ingredient,'" 35 U.S.C. § 156(f) "clearly provides" that the active ingredient itself cannot be a salt or an ester. 359 F.3d at 1365-66. Instead, the Court held that "active ingredient" means "active moiety." *Id.* at 1366. The Court relied on the FDA's marketing exclusivity regulations, which equate "active ingredient" with "active moiety" and

define "active moiety" as "'the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester [or] salt * * * responsible for the physiological or pharmacological action of the drug substance.'" *Id.* at 1366 (quoting 21 C.F.R. § 314.108(a)).

Pfizer also observed that "[t]he statute foresaw variation in the salt or ester of an active ingredient, and guarded against the very loophole now urged [by Dr. Reddy's]" by including salts and esters of the active ingredient within the definition of "drug product." 359 F.3d at 1366, citing 35 U.S.C. 156(f) and 21 U.S.C. 355(j)(5)(D)(i) and (v) (now codified as 21 U.S.C. 355(j)(5)(F)(i) and (v)). The operation of the patent term extension provision, the Court said, "was not intended to be defeated by simply changing the salt [or ester]." *Id.* at 1366. To permit otherwise would allow a manufacturer to obtain approval of its own product based on the pioneer manufacturer's "approved uses and data" and do so by merely changing a salt or ester and, at the same time, would "ba[r] extension of patent coverage of the drug product whose approvals and data" were the basis for the subsequent product's approval. *Id.* at 1366.[8]

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[8] The *Pfizer* Court agreed with Pfizer "that a changed salt does not affect the therapeutically active agent, which is the same amlodipine, whatever the salt," 359 F.3d at 1365, and agreed "that the active ingredient is amlodipine, and that it is the same whether administered as the besylate salt or the maleate salt." 359 F.3d at

(continued...)

In short, *Pfizer* squarely addresses the meaning of "active ingredient" in Section 156 and construes it to refer to the drug's active moiety. That is precisely the interpretation that USPTO employs, and the agency relied on that interpretation in granting Ortho-McNeil's patent term extension application in this case. Under *Pfizer*, that determination — for which the USPTO is entitled to "great deference," see A25 (quoting *Pfizer, Inc. v. Ranbaxy Labs Ltd.*, 457 F.3d 1284, 1290 (Fed. Cir. 2006), which, in turn, quoted *Glaxo*, 894 F.2d at 399)) — must be sustained.

Ortho-McNeil argues that *Pfizer* is not controlling because it involved the scope of an extension under Section 156(b), not eligibility for an extension under Section 156(a). See Ortho-McNeil Br. at 35. But Section 156(f)'s definitions apply to Section 156 in its entirety. See 35 U.S.C. 156(f) ("For purposes of this section * * * [t]he term 'product' means * * * "). Hence, there is no room for Ortho-McNeil's suggestion that "active ingredient" means "active moiety" under Section 156(b) but something else under Section 156(a).

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[8](...continued)
1366. Cf. *Merck & Co., Inc. v. Teva Pharmaceuticals USA, Inc.*, 347 F.3d 1367 (Fed. Cir. 2003) (finding "active moiety" key to patent infringement and patent term extension issues).

2. While Lupin appears to recognize that *Pfizer* is this Court's governing precedent regarding the meaning of "active ingredient" under Section 156, Ortho-McNeil argues that the controlling decision is *Glaxo* instead. *Compare* Lupin Opening Br. at 29, 34 (citing *Pfizer*),[9] *with* Ortho-McNeil Br. at 14-15, 23, 32-36 (citing *Glaxo*).[10] But the meaning of "active ingredient" was not in dispute in *Glaxo*.[11] To the contrary, the parties in *Glaxo* agreed on the active ingredient in that case, and the appeal was litigated on the basis of that common understanding. As a consequence, the Court reviewed USPTO's patent term extension decision without ever addressing, or having any occasion to address, the meaning of "active ingredient."

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[9] But see Lupin Reply Br. at 13 ("Lupin is not arguing that this Court must interpret the 'active ingredient' language in § 156 to mean 'active moiety.'")

[10] Notwithstanding the fact that Lupin would be correct to rely on *Pfizer* and Ortho-McNeil is incorrect to rely on *Glaxo*, it is the government's view that the proper application of *Pfizer* leads to affirmance of the district court's decision.

[11] Both Lupin and Ortho-McNeil also appear to argue — erroneously — that FDA regulations are controlling. See Lupin Opening Br. at 14 (citing 21 C.F.R. 60.3(b)(2) and 21 C.F.R. 210.3(b)(7))); and Ortho-McNeil Br. at 20-22 (same). FDA regulations are not controlling; USPTO is charged with administering the patent term extension provisions. See pp. 1-2, *supra*. Thus, if *Pfizer* itself is not controlling, USPTO's administrative interpretation — which happens to be consistent with *Pfizer* — is.

Glaxo was seeking a patent term extension for cefuroxime axetil — an ester of the acid cefuroxime, which is the active moiety. 894 F.2d at 393-94. Today, the USPTO's position would be that cefuroxime, the active moiety, is the "active ingredient." At the time of the *Glaxo* appeal, however, USPTO took the position that the active ingredient was cefuroxime axetil, the ester of the active moiety. *Id.* at 394.[12] For its part, Glaxo took precisely the same position. *Ibid.*

Because the USPTO and Glaxo were in agreement that the "active ingredient" was cefuroxime axetil, the parties' arguments focused solely on whether the term "product" in Section 156(a)(5) — limiting a term extension to the "the [first] commercial marketing or use of the product after such regulatory review period" — meant the precise product approved by the FDA. Thus, the court focused solely on whether cefuroxime axetil, Glaxo's "product," was the same as a product previously approved by FDA for commercial marketing. The court noted that the precise products previously approved by the FDA were salts

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[12] In the proceedings before the district court in *Glaxo*, USPTO did advance the active moiety reading of "active ingredient." See *Glaxo Operations UK Limited v. Quigg*, 706 F.2d 1224, 1226 (E.D. Va. 1989), *aff'd*, 894 F.2d 392 (Fed. Cir. 1990). However, the USPTO had not relied on that reading at the administrative stage. On appeal, the USPTO acknowledged that *Chenery* principles (see *SEC v. Chenery Corp.*, 332 U.S. 194, 196-197 (1947)) foreclosed the agency from relying on a post hoc interpretive rationale, and therefore did not seek to defend its administrative decision on the basis of the active moiety interpretation.

of cefuroxime, whereas Glaxo's product (cefuroxime axetil) was an ester of cefuroxime and the previously approved products were neither salts nor esters of cefuroxime axetil (Glaxo's product). See 894 F.2d at 393-94. The court decided, therefore, that cefuroxime axetil had not been previously approved by the FDA, and affirmed the district court's grant of a patent term extension which had overruled the USPTO's denial of the extension. In so doing, this Court never addressed the meaning of "active ingredient" or the precise role that that definition plays in the patent term extension regime. *Id.* at 394-400.

It is telling in this regard that the Court's decision in *Pfizer* never mentions *Glaxo*. This omission can hardly have been an oversight, for the appellate briefs,[13] the petition for rehearing en banc,[14] and the rehearing response[15] all featured *Glaxo* prominently, with the generic manufacturer in *Pfizer* arguing that *Glaxo* was controlling and Pfizer arguing the opposite. The fact that *Glaxo* was never mentioned in *Pfizer* — not even in Judge Mayer's dissent — confirms that *Glaxo*, properly understood, does not address the meaning of "active ingredient" in

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[13] See 2003 WL 24032076 (appellant's opening brief), 2003 WL 24032075 (appellee's brief), and 2003 WL 24032077 (appellant's reply brief).

[14] See 2004 WL 3261083.

[15] See 2004 WL 3261016.

Section 156, and hence that *Pfizer* is the controlling precedent as to the meaning of that term. Thus, Ortho-McNeil's argument that *Glaxo* is controlling because the later *Pfizer* decision could not overrule *Glaxo* (see Ortho-McNeil Br. at 34) is without merit; there was nothing in *Glaxo* for *Pfizer* to overrule.

B. Even if *Pfizer* Does not Control, the USPTO's Interpretation is Persuasive and Should be Upheld.

1. Even if *Pfizer* were not considered controlling, the USPTO's interpretation of "active ingredient" in 35 U.S.C. 156 is persuasive and should be upheld. We summarize the principal grounds for the USPTO's interpretation in this amicus brief; the government's forthcoming brief in *PhotoCure*, where the issue is raised more directly, will explain the agency's reasoning in greater detail.

As noted above, 35 U.S.C. 156(f)(2)(A) defines "drug product" to mean (in pertinent part) "the active ingredient of * * * a new drug, * * * including any salt or ester of the active ingredient," but it does not define "active ingredient." To determine what the statute means by "active ingredient," USPTO reads the definition of "drug product" to encompass three categories of molecules: (1) the non-salified and non-esterified form of a molecule, (2) any salt of that molecule; and (3) any ester of that molecule. USPTO Final Decision in *PhotoCure* (May 13, 2008) at 3 (attached hereto as Addendum B). Parsing the language, the USPTO

interprets "active ingredient" to refer to the first category of molecules, which is the "active moiety" of the drug — the pharmacologically active molecule to which components can be added to make it a salt or ester. In *Pfizer*, the Court reasoned similarly, reading the reference to "any salt or ester of the active ingredient" as an indication that Congress did not conceive of individual salts and esters as themselves constituting active ingredients. *Pfizer*, 359 F.3d at 1365-66. See also discussion, *supra*, at 16-19.

As a textual matter, if "active ingredient" is understood to mean active moiety, it is entirely coherent to speak of salts and esters of the active moiety. Such a reading, moreover, makes sense of the "including" clause, which, by its presence, indicates that the "active ingredient" is a form of the molecule that does not "include" the components that would make it a salt or ester — in other words, the "active moiety."

2. As further support for the persuasiveness of the USPTO's interpretation, it is significant that the FDA, which is faced with virtually identical statutory language in administering the market exclusivity provisions of Title I of the Hatch-Waxman Act, has adopted the same reading of "active ingredient" that the USPTO employs here. Under the marketing exclusivity provisions of the Hatch-Waxman Act, FDA is required to grant periods of marketing exclusivity to a newly

approved drug if that drug contains no "active ingredient (including any ester or salt of the active ingredient)" that has received prior FDA approval. See 21 U.S.C. 355(j)(5)(F)(i), (ii), and (v) (formerly 355(j)(4)(D)(i), (ii), and (v)). In that context, where the statutory language refers to "active ingredient" in conjunction with the parenthetical, "any ester or salt of the active ingredient," the FDA has expressly interpreted "active ingredient" to mean "active moiety." See 59 Fed. Reg. 50338, 50358 (1994) (explaining agency's use of "active moiety" in marketing exclusivity regulations).

In contrast, when construing other provisions of the Hatch-Waxman Act that refer to "active ingredient" *without* the salt/ester parenthetical (see 21 U.S.C. 355(j) (2) (A)), FDA has construed "active ingredient" to mean "the active ingredient in the finished drug product *prior to its administration,*" 54 Fed. Reg. 28872, 28881 (1989) (2d col.) (1989) (emphasis added), which *may not necessarily be* the "active moiety" (*i.e.*, the molecule that delivers the pharmacological effect *after* administration). In short, FDA treats the phrase "active ingredient" when directly linked to the salt/ester parenthetical as having a different meaning than "active ingredient" standing alone and, like USPTO, as meaning the "active moiety." Thus, contrary to the contentions of both Lupin (Opening Br. at 25-26) and Ortho-McNeil (Br. at 22, 33), there was no settled

administrative understanding of what "active ingredient" meant in the specific statutory context presented in this case.

Ortho-McNeil cites an informal document on the FDA website, "Frequently Asked Questions on the Patent Term Restoration Program," in which the FDA states that, for purposes of its own patent term extension regulation, 21 C.F.R. 60.3(b)(2), "[a]ctive ingredient does not equal active moiety * * *." Ortho-McNeil Br. at 36. As just noted, the FDA interprets "active ingredient" differently when the same language — "active ingredient (including any ester or salt of the active ingredient)" — is used in the marketing exclusivity provisions. There, when the parenthetical is present, FDA has concluded that "active ingredient" *does* equal "active moiety." The divergent interpretation reflected in FDA's online document appears to be based on the assumption that *Glaxo* requires that interpretation in the context of Section 156. See, *e.g.*, A21 (FDA's response to USPTO's request for advice on the "first permitted commercial marketing or use" cites *Glaxo* as the controlling authority for its determination). But as shown above, that assumption is incorrect; and, when the same language is linked to the salt/ester parenthetical, the FDA construes "active ingredient" precisely the same way the USPTO does.

3. There is no legislative history directly addressing the meaning of "active ingredient." However, at a more general level, the legislative history strongly

suggests that Congress wanted to reward truly innovative research involving "new chemical entities" with patent term extensions, but did not intend to reward drug products with patent term extensions where the approval of those products was based on new uses, dosage forms, or formulations of previously approved drug products. See USPTO Final Decision in *PhotoCure* at 4. In *Fisons v. Quigg*, 1988 WL 150851 (D.D.C. 1988), *aff'd*, 876 F.2d 99 (Fed. Cir. 1989), the district court noted:

> Upon examination, the specific purpose of Section 156(a)(5)(A) appears to have been relatively narrow — to restore lost patent life only for "pioneer" drugs. A report by the Congressional Office of Technology Assessment ("OTA") to the 97th Congress provided the factual foundation for the restriction of patent restoration benefits to new chemical entities. The OTA report stated: "Although important pharmaceutical innovations may result from new therapeutic applications of existing chemicals * * * many of the pharmaceutical breakthroughs that have occurred have resulted from NCE (new chemical entity) research and the development of NCEs generally has required more time and money than other types of innovation and has involved greater risks." The House Committee on Energy and Commerce explained that the bill "requires extensions to be based on the first approval of the product because the only evidence available to Congress showing that patent time has been lost is data on so-called class I, new chemical entity drugs."

1988 WL 150851 at *7. Thus, "Congress's intent was to restore patent life only to new chemical entities." *Ibid.*

In the USPTO's view, providing a patent term extension to a drug whose active moiety is the same as that of a previously approved drug is not rewarding genuine innovation and would, therefore, be inconsistent with congressional intent. Accord, *Pfizer*, 359 F.3d at 1366 ("None of the aspects offered to the district court or on this appeal suggests a statutory intent to provide the generic producer with access to the pioneer's approved uses and data while barring extension of patent coverage of the drug product whose approvals and data are provided."). Accordingly, even if other interpretations are possible, USPTO's interpretation — which, consistent with Congress's intent, rewards only innovators — should prevail.

4. In *PhotoCure*, 2009 WL 855807, the district court concluded that the dictionary definition of the word "ingredient" requires that the active ingredient actually be contained in the final compound. See 2009 WL 855807 at *8, citing 7 Oxford English Dictionary 963-64 (2d ed. 1989) (an "ingredient" is "[s]omething that enters into the formation of a compound or mixture; a component part, constituent or element."). See also *Glaxo*, 706 F. Supp. at 1227-28 (same). In the *PhotoCure* court's view, a plain meaning interpretation of the term "active ingredient" requires the actual presence of a compound qualifying as the "active ingredient" in the drug — an interpretation that would preclude equating "active

ingredient" with active moiety, since the active moiety may not be present in the drug in its non-esterified and non-salified form.

The *PhotoCure* court, however, misunderstood the dictionary definition. An ingredient can "*enter[] into the formation* of a compound or mixture," 7 Oxford English Dictionary at 963-64 (emphasis added), without actually being present in the final product. For example, a bottle of beer does not contain hops or yeast, yet no one would dispute that hops and yeast are ingredients of beer, since they are two of the principal components used to create it. Thus, nothing in the dictionary definition of "ingredient" suggests that a component cannot be an ingredient of a drug product *unless* it is physically present in the finished product. Therefore, any contention that a component must be present in the drug product to qualify as an "active ingredient" is wrong.

5. Finally, if "active ingredient" were not construed to mean "active moiety," the eligibility for a patent term extension could turn on the sequence of drug approvals, not innovation. If the originally approved drug product was a salt or acid and the new drug approval is for an ester form of the acid, an extension would be granted, but if the originally approved drug was an acid and the new drug product is a salt or ester form of the acid, the extension would be denied. See, *e.g.*, *Glaxo*, 706 F. Supp. at 1229-30 n.12. There is no apparent legislative

purpose for that odd, "asymmetrical" result. *Ibid.* See also *Abbott Labs. v. Young*, 920 F.2d 984, 989 (D.C. Cir. 1990) (to have patent term extensions depend on the sequence of drug approvals "fail[s] to serve any conceivable statutory purpose"). Indeed, as previously noted, it contradicts Congress's intent to reward only truly innovative research. See pp. 26-28, *supra*.[16] Construing "active ingredient" to mean active moiety avoids this irrational regulatory asymmetry.

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[16] *Glaxo* stated that "the development of an innovative ester or salt from the acid may be worthier of reward because many different salts or esters may derive from a single acid and it is, not infrequently, more difficult to find an innovative salt or ester from the acid." 706 F. Supp. at 1229-30 n.12. We are not aware of any support for that statement.

CONCLUSION

For the foregoing reasons, the term "active ingredient" in 35 U.S.C. 156(f) means "active moiety," and based on that interpretation, the judgment of the district court should be affirmed.

Respectfully submitted,

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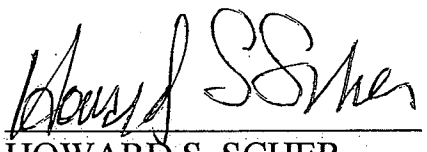
CERTIFICATE OF COMPLIANCE WITH RULE 32(a)
OF THE FEDERAL RULES OF APPELLATE PROCEDURE

1. Pursuant to Fed. R. App. P. 32(a)(7), I certify that the attached **BRIEF FOR THE UNITED STATES AS AMICUS CURIAE IN SUPPORT OF THE APPELLEES** complies with the type-volume limitation of Fed. R. App. P. 29(d) and 32(a)(7)(B). The brief contains **6,727** words, as counted by Word Perfect 12, excluding the parts of the brief exempted by Fed. R. App. P. 32(a)(7)(B)(iii) and Federal Circuit Rule 32(b).

2. I also certify that this brief complies with the typeface requirements of Fed. R. App. P. 32(a)(5) and the type style requirements of Fed. R. App. P. 32(a)(6). The brief has been prepared in a proportionally-spaced typeface using Word Perfect 12 in 14-point Times New Roman.



HOWARD S. SCHER
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ADDENDUM A

35 U.S.C. 156, in pertinent part, provides as follows:

(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--

(1) the term of the patent has not expired before an application is submitted under subsection (d)(1) for its extension;

(2) the term of the patent has never been extended under subsection (e)(1) of this section;

(3) an application for extension is submitted by the owner of record of the patent or its agent and in accordance with the requirements of paragraphs (1) through (4) of subsection (d);

(4) the product has been subject to a regulatory review period before its commercial marketing or use;

(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.

(B) Any medical device, food additive, or color additive subject to regulation under the Federal Food, Drug, and Cosmetic Act.

(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

(B) a new animal drug or veterinary biological product (as those terms are used in the Federal Food, Drug, and Cosmetic Act and the Virus-Serum-Toxin Act) which is not primarily manufactured using recombinant DNA, recombinant RNA, hybridoma technology, or other processes involving site specific genetic manipulation techniques,

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

ADDENDUM B

UNITED STATES PATENT AND TRADEMARK OFFICE

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MAY 13 2008

Kenyon & Kenyon
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In Re: Patent Term Extension
Application for
U.S. Patent No. 6,034,267

FINAL DECISION REGARDING PATENT TERM EXTENSION APPLICATION UNDER 35 U.S.C. § 156 FOR U.S. PATENT NO. 6,034,267

This is in response to the application for extension of the term of U.S. Patent No. 6,034,267 ("the '267 patent") filed under 35 U.S.C. § 156 in the United States Patent and Trademark Office ("USPTO") on September 22, 2004 ("the PTE Application"), and the Request for Reconsideration of Final Determination of Ineligibility for Patent Term Extension filed on November 13, 2007 ("the Request for Reconsideration"). The PTE Application was filed by PhotoCure ASA ("Applicant"), assignee and owner of the '267 patent. Extension was sought based upon the premarket review of METVIXIA™ (methyl aminolevulinate hydrochloride) under section 505(b) of the Federal Food Drug and Cosmetic Act ("FFDCA"). Because the Food and Drug Administration ("FDA") and the USPTO have determined that the approval of METVIXIA™ (methyl aminolevulinate hydrochloride) does not constitute the first permitted commercial marketing or use of the "product," the PTE Application is **DENIED** and the Request for Reconsideration is **DENIED**.

A. Factual Background

On July 27, 2004, the FDA approved NDA No. 21-415 for METVIXIA™ (methyl aminolevulinate hydrochloride).

On September 22, 2004, Applicant timely filed the PTE Application in the USPTO.

On November 7, 2006, the USPTO sent a letter to FDA, requesting the FDA's assistance in confirming that (1) the product identified in the PTE Application, METVIXIA™ (methyl aminolevulinate hydrochloride), was subject to a regulatory review period within the meaning of 35 U.S.C. § 156(g) before its first permitted commercial marketing or use and (2) the PTE application was filed within the sixty-day period beginning on the date the product received permission under the provision of law under which the applicable regulatory review period occurred for commercial marketing or use, as required by 35 U.S.C. § 156(d)(1). The November 7, 2006, letter notes at page 2 that "[a]minolevulinic acid hydrochloride had been previously approved by the FDA" and that "methyl aminolevulinate hydrochloride is an ester of aminolevulinic acid hydrochloride."

On March 5, 2007, FDA responded to the USPTO stating (1) FDA's approval of

METVIXIA™ (methyl aminolevulinate hydrochloride) does not represent the first permitted commercial marketing or use of the "product," as defined under 35 U.S.C. § 156(f)(1), and as interpreted by the courts, and (2) the PTE Application was timely filed.

On April 11, 2007, the USPTO mailed a Notice of Final Determination – Ineligible ("Notice") in which the USPTO states that the '267 patent is ineligible for patent term extension under 35 U.S.C. § 156. In particular, the Notice states:

> By the explicit terms of section 156(f)(2), the term "product" as it relates to a human drug product means the active ingredient of the new drug product. The active ingredient in the approved product METVIXIA™ is methyl aminolevulinate hydrochloride, which, as an ester of the previously-approved aminolevulinic acid hydrochloride, is by statute the same product as aminolevulinic acid hydrochloride. ... Furthermore, the prior approval of the active ingredient aminolevulinic acid hydrochloride in LEVULAN® by the Food and Drug Administration was under section 505 of the FFDCA, the same provision of law under which regulatory review of the product METVIXIA™ occurred.

On November 13, 2007, Applicant filed the Request for Reconsideration. The Request for Reconsideration states at page 3 that "the proper inquiry is simply, based on the plain language of the statute, whether or not the active ingredient in Levulan®, namely, aminolevulinic acid hydrochloride, is an ester (or the same as or a salt) of the active ingredient of Metvixia™." The Request for Reconsideration further states the following, at the paragraph bridging pages 3 and 4:

> the active ingredient of Metvixia™ is the hydrochloride salt of the ester methyl aminolevulinate, whereas the active ingredient of Levulan® is the hydrochloride salt of the acid aminolevulinic acid. Aminolevulinic acid hydrochloride is not the same as, or a salt or ester of, methyl aminolevulinate hydrochloride. The product methyl aminolevulinate hydrochloride therefore has not been previously approved because aminolevulinic acid hydrochloride does not "[fall] within the definition" of "product" as that term is properly construed. *See* [*Glaxo Operations UK, Ltd v. Quigg*, 894 F.2d 392, 394 (Fed. Cir. 1990)]. It therefore follows that Metvixia™ is not precluded from patent term extension eligibility by the previous approval of aminolevulinic acid hydrochloride.

(Emphasis in the original). The Request for Reconsideration also states at page 5 that "there are substantial differences between methyl aminolevulinate hydrochloride and [5-aminolevulinic acid ("ALA")] hydrochloride, as evidenced by the attached Declaration of Dr. Kristian Berg in Support of Grant of Patent Term Extension with Respect to U.S. Patent No. 6,034,267 and accompanying exhibits."

B. Decision

1. The Plain Language of 35 U.S.C. § 156(f) Shows That METVIXIA™ (methyl aminolevulinate hydrochloride) Is Not the First Permitted Commercial Marketing or Use of the "Product" As Required by 35 U.S.C. § 156(a)(5)(A)

Section 156(a) of Title 35 sets forth several requirements that must be met before the Director can extend the term of a patent. *See* 35 U.S.C. §§ 156 (a)(1)-(a)(5), (d)(1), & (e)(1). Section 156(a)(5)(A) requires that:

> the permission for the commercial marketing or use of the product ... [be] the first permitted commercial marketing or use of the product under the provision of law under which such regulatory review period occurred.

(Emphasis added). The term "product" as used in section 156(a)(5)(A) is defined in section 156(f)(1) as a "drug product," and the term "drug product" is defined in section 156(f)(2) as the "active ingredient of [a] new drug, antibiotic drug, or human biological product ... 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) (emphasis added). Hence, by the explicit terms of section 156(f)(2), the term "product" as used in section 156 includes: (i) a non-salified and non-esterified form of a molecule (*i.e.*, the "active ingredient"); (ii) any salt of the molecule (*i.e.*, the "salt ... of the active ingredient"); and (iii) any ester of the molecule (*i.e.*, the " ... ester of the active ingredient").[1] Because a "product" includes all three forms, any salt of a molecule is statutorily the same "product" as any ester of the molecule for purposes of the patent term extension provisions in section 156. Further, the plain meaning of the phrase "any ester" encompasses any ester, including salified and non-salified esters.

Prior to the approval of METVIXIA™ (methyl aminolevulinate hydrochloride), the FDA approved LEVULAN® (aminolevulinic acid hydrochloride). There is no dispute that ALA is present in both METVIXIA™ and LEVULAN® as the underlying molecule. For example, at page 2 of the Declaration attached to the Request for Reconsideration, Dr. Berg states that METVIXIA™ "has as its active ingredient the hydrochloride salt of the methyl ester of ALA," and that LEVULAN® "has the hydrochloride salt of ALA as its active ingredient." Consequently, the approved "product" is the same for both METVIXIA™ and LEVULAN® under section 156, *i.e.*, ALA merely formulated differently in each product. The later approved METVIXIA™ (methyl aminolevulinate hydrochloride) thus does not represent the first permitted commercial marketing or use of the "product" under the provision of law under which such regulatory review occurred. The USPTO therefore concludes that the PTE Application does not

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[1]The plain language of section 156(f) makes clear that the same definition of "product" is to be applied throughout section 156. Section 156(f) explicitly states that its provisions are "for purposes of this section." Thus, the term "product" as used throughout 35 U.S.C. § 156—for eligibility under section 156(a) and for enforcement under section 156(b)—has but one meaning.

satisfy the requirement of section 156(a)(5)(A) and the '267 patent is ineligible for a patent term extension. Accordingly, the PTE Application must be **DENIED**.

2. Judicial Precedent Confirms That METVIXIA™ (methyl aminolevulinate hydrochloride) Is Not the First Permitted Commercial Marketing or Use of the "Product" As Required by 35 U.S.C. § 156(a)(5)(A)

Judicial precedent confirms that the USPTO's application of the definition of "product," as that term is used in section 156(a)(5)(A), is correct. In *Fisons v. Quigg*, 1988 WL 150851 (D.D.C. 1988) ("*Fisons I*"), the district court addressed the meaning of the term "product." The district court considered both the plain language of section 156(a)(5)(A) and its legislative history. With respect to the latter, the district court observed:

> Upon examination, the specific purpose of Section 156(a)(5)(A) appears to have been relatively narrow—to restore lost patent life only for "pioneer" drugs. A report by the Congressional Office of Technology Assessment ("OTA") to the 97th Congress provided the factual foundation for the restriction of patent restoration benefits to new chemical entities. The OTA report stated: "Although important pharmaceutical innovations may result from new therapeutic applications of existing chemicals ... many of the pharmaceutical breakthroughs that have occurred have resulted from NCE (new chemical entity) research and the development of NCEs generally has required more time and money than other types of innovation and has involved greater risks." The House Committee on Energy and Commerce explained that the bill "requires extensions to be based on the first approval of the product because the only evidence available to Congress showing that patent time has been lost is data on so-called class I, new chemical entity drugs."

Fisons I, 1988 WL 150851 at *7. After making these observations, the district court found that "Congress's intent was to restore patent life only to new chemical entities." The district court thus construed section 156(a)(5)(A) in a straightforward way:

> In the definitional provision of Section 156, the term "product" is defined as a "human drug product." 35 U.S.C. § 156(f)(1)(A). This term is further defined in the next subparagraph as "the *active ingredient* of a new drug, antibiotic drug, or human biological product ... 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 in original). Substituting this definition directly back into Section 156(a)(5)(A) yields the statement that 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.

Id. at *5.

The Federal Circuit affirmed the district court's interpretation. *See Fisons v. Quigg*, 876 F.2d 99 (Fed. Cir. 1989) ("*Fisons II*"). The Federal Circuit stated: "In sum, we hold that the district court correctly applied the definition given in 35 U.S.C. § 156(f) to the term 'product' used in section 156(a)(5)(A). We are convinced that such an interpretation comports with the intent of Congress as expressed in the statute." *Fisons II*, 876 F.2d at 102.

The Federal Circuit later interpreted the term "active ingredient" in *Pfizer, Inc. v. Dr. Reddy's Labs.*, Ltd., 359 F.3d 1361 (Fed. Cir. 2004). There, the Federal Circuit accepted the FDA's definition of the term "active ingredient" as meaning "active moiety." *See id.* at 1366 (citing Abbreviated New Drug Application Regulations: Patent and Exclusivity Provisions, 59 Fed. Reg. 50,338, 50,358 (F.D.A. Oct. 3, 1994)). It likewise accepted that "active moiety" means "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," based upon the FDA's regulations. *Id.* (quoting 21 C.F.R. § 314.108(a)) (omission in original). Hence, the Federal Circuit has construed the term "active ingredient" as used in section 156(f)(2) to mean the underlying molecule, *i.e.*, the molecule or ion responsible for the physiological or pharmacological action of the drug, excluding those appended portions of the molecule that cause the drug to be an ester or salt.

Substituting this definition for the word "active ingredient" as it appears in section 156, the term "drug product" in section 156(f)(2) must mean the underlying molecule as well as any salt or ester of the underlying molecule, since it is defined as "active ingredient ... including any salt or ester of the active ingredient." Further, because "product" is defined as "drug product" in section 156(f)(1)(A), "product" likewise must mean the underlying molecule as well as any salt or ester of the underlying molecule. That definition conforms with the plain language of section 156(f). What is more, the Federal Circuit confirmed in *Pfizer* that only the first approval for any given "active ingredient" can trigger a patent term extension under 35 U.S.C. § 156, regardless of whether that first approval was for an underlying molecule, a salt of the underlying molecule, or an ester of the underlying molecule. *See Pfizer*, 359 F.3d at 1366 ("The statute [referring to 35 U.S.C. § 156] foresaw variation in the salt or ester of an active ingredient, and guarded against the very loophole now urged.").

Here, before approving METVIXIA™ (methyl aminolevulinate hydrochloride) in 2004, the FDA approved LEVULAN® (aminolevulinic acid hydrochloride) in 1999. As explained above, ALA is the underlying molecule in both METVIXIA™ and LEVULAN®. ALA is simply formulated differently in the two different drugs: as a hydrochloride salt of its methyl ester in METVIXIA™, and as a hydrochloride salt in LEVULAN®. However, the difference in formulation does not matter for purposes of defining a product in section 156. The statutory definition of "product" includes the underlying molecule as well as any salt or ester of the underlying molecule. Accordingly, METVIXIA™ (methyl aminolevulinate hydrochloride) is not the first permitted commercial marketing or use of the "product" as required by 35 U.S.C. § 156(a)(5)(A) because of the earlier approval of LEVULAN® (aminolevulinic acid hydrochloride).

Finally, the FDA has issued a regulation defining the term "active ingredient" of a pharmaceutical "product" for purposes of patent term extension under 35 U.S.C. § 156. Specifically, 21 C.F.R. § 60.1(a) states that "[t]his part [referring to Part 60] sets forth procedures and requirements for the [FDA]'s review of applications for the extension of the term of certain patents under 35 U.S.C. § 156." That provision further states that "[FDA] actions in this area include [*inter alia*] [a]ssisting the [USPTO] in determining eligibility for patent term restoration." 21 C.F.R. § 60.1(a)(1). Section 60.3 then provides a series of definitions to be used in Part 60 in addition to the definitions already contained in 35 U.S.C. § 156. 37 C.F.R. § 60(b)(2) defines "active ingredient" for purposes of a patent extension to mean a drug's active moiety, *i.e.*, its therapeutically active component. It states:

> Active ingredient means any component that is intended to furnish pharmacological activity or other direct effects in the diagnosis, cure, mitigation, treatment or prevention of disease, or to affect the structure or function of the body of man or of animals. The term includes those components that may undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect.

21 C.F.R. § 60.3 (b)(2). Applying the FDA's regulations in this case, ALA is the "active ingredient" of not just LEVULAN® (aminolevulinic acid hydrochloride), but also of METVIXIA™ (methyl aminolevulinate hydrochloride); it is simply formulated as a hydrochloride salt of its methyl ester in METVIXIA™, and as a hydrochloride salt in LEVULAN®.

The USPTO recognizes that *Glaxo* also concerns section 156(f). However, the USPTO observes that *Glaxo* is factually distinguishable because the Federal Circuit did not address the definition of "active ingredient" in that case. Rather, the Federal Circuit focused on the USPTO's argument that the term "product" did not have the literal meaning set forth in section 156(f)(2), but instead meant "any 'new chemical entity,' *i.e.*, 'new active moiety.'" Rejecting that argument, the Federal Circuit explained that Congress provided a definition of the term "product" in section 156(f)(2) and that Congress "selected terms with narrow meanings that it chose from among many alternatives." *Glaxo*, 894 F.2d at 399 (footnoting as examples of other possible words "new molecular entity," "active moiety," and "new chemical entity"). The Federal Circuit did not discuss the definition of the term "active ingredient" because, unlike here, the determination of the active ingredient was not in dispute in *Glaxo*.

The most that can be said about *Glaxo* is that the Federal Circuit acknowledged that the term "product" was not expressly defined by Congress to mean "active moiety," since those words do not appear in section 156(f)(2). However, *Glaxo* does not hold that the term "active ingredient" as used in section 156(f)(2) does not mean "active moiety." In fact, the Federal Circuit later accorded the term "active ingredient" with that precise definition in *Pfizer*. *See Pfizer*, 359 F.3d at 1366. Accordingly, the USPTO's determination that the '267 patent is

ineligible for extension pursuant to section 156 is supported by, and consistent with, *Glaxo*. As such, the PTE Application must be **DENIED**.

3. Applicant's Argument That METVIXIA™ Is Eligible for Patent Term Extension Because Neither Methyl Aminolevulinate Hydrochloride nor Any Salt or Ester of Methyl Aminolevulinate Hydrochloride Has Been Previously Approved for Commercial Marketing or Use Is Unpersuasive

Applicant states at page 3 of the Request for Reconsideration that "the proper inquiry is simply, based on the plain language of the statute, whether or not the active ingredient in Levulan®, namely, aminolevulinic acid hydrochloride, is an ester (or the same as or a salt) of the active ingredient of Metvixia™." At the paragraph bridging pages 3 and 4 of the Request for Reconsideration, Applicant concludes that the '267 patent is eligible for extension, because "[a]minolevulinic acid hydrochloride is not the same as, or a salt or ester of, methyl aminolevulinate hydrochloride."

In making the above statements in the Request for Reconsideration, Applicant ignores both (i) the full scope of the relationship between aminolevulinic acid hydrochloride and methyl aminolevulinate hydrochloride, and (ii) the Federal Circuit's decision in *Pfizer* that the term "active ingredient," when properly construed, means the underlying molecule, *i.e.*, the molecule or ion responsible for the physiological or pharmacological action of the drug, excluding those appended portions of the molecule that cause the drug to be an ester or salt. Applying the Federal Circuit's construction of the term "active ingredient" in *Pfizer* to the present case, ALA is the "active ingredient" of both METVIXIA™ and LEVULAN®. Consequently, the active ingredient in METVIXIA™ - ALA formulated as a hydrochloride salt of its methyl ester - has already been approved by the FDA with the approval of LEVULAN® (ALA formulated as a hydrochloride salt). Applicant's statement that neither methyl aminolevulinate hydrochloride nor an ester or salt of methyl aminolevulinate hydrochloride had previously been approved, while correct, is irrelevant to the calculus here. The USPTO must therefore conclude that the PTE Application does not satisfy the requirement of section 156(a)(5)(A) and the '267 patent is ineligible for a patent term extension. Accordingly, the PTE Application must be **DENIED**.

4. Applicant's Argument That There Are Substantial Differences Between Methyl Aminolevulinate Hydrochloride and Aminolevulinic Acid Hydrochloride Is Unpersuasive

Applicant states the following at page 5 of the Request for Reconsideration:

> there are substantial differences between methyl aminolevulinate hydrochloride and ALA hydrochloride, as evidenced by the attached Declaration of Dr. Kristian Berg in Support of Grant of Patent Term Extension with Respect to U.S. Patent

No. 6,034,267 and accompanying exhibits. These include substantial differences in selectivity of uptake by target lesions, penetration of target lesions, (unwanted) systemic distribution, pain resulting from use in PDT, and mechanisms of cell uptake. Accordingly, methyl aminolevulinate hydrochloride should not be considered the same "product" as aminolevulinic acid hydrochloride (regardless of how "product" is construed).

The existence of "substantial differences" between methyl aminolevulinate hydrochloride and aminolevulinic acid hydrochloride, even if verified, has no bearing on whether the PTE Application satisfies the requirement of section 156(a)(5)(A). For the reasons stated in the analysis above, the approved "product" is the same for both METVIXIA™ and LEVULAN® under section 156, *i.e.*, ALA merely formulated differently in each product. Nothing in the statutory language of 35 U.S.C. § 156 or in judicial precedent considering section 156 creates a "substantial differences" exception in the inquiry of whether the requirement of section 156(a)(5)(A) has been satisfied. For the reasons stated earlier herein, the USPTO concludes that the PTE Application does not satisfy the requirement of section 156(a)(5)(A) and the '267 patent is ineligible for a patent term extension. Therefore, the PTE Application must be **DENIED**.

5. Conclusion

For the reasons stated above, Applicant's request for extension of the patent term of the '267 patent is **DENIED**, and Applicant's Request for Reconsideration is **DENIED**.

This is considered a final agency decision.

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Attention: Beverly Friedman

RE: METVIXIA™ (methyl aminolevulinate hydrochloride)
FDA Docket No.: 2007E-0001