**IN THE UNITED STATES DISTRICT COURT FOR THE EASTERN DISTRICT OF VIRGINIA**
**Alexandria Division**

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| PHOTOCURE ASA,<br>Plaintiff,<br><br>v.<br><br>JON W. DUDAS,<br>Under Secretary of Commerce for Intellectual Property and Director of the United States Patent and Trademark Office,<br>and JOHN J. DOLL, Commissioner for Patents,<br><br>Defendants. | Civil Action No. 1:08CV718-LO/JFA |

**PLAINTIFF PHOTOCURE ASA'S MEMORANDUM IN SUPPORT OF ITS MOTION FOR SUMMARY JUDGMENT THAT ITS U.S. PATENT NO. 6,034,267 SHOULD BE EXTENDED UNDER 35 U.S.C. § 156**

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## INTRODUCTION

This is a patent case brought by plaintiff Photocure ASA ("Photocure") under the Administrative Procedure Act. Photocure seeks to have this Court hold unlawful and set aside the decision by defendants Jon W. Dudas, Director of the United States Patent and Trademark Office, and John J. Doll, Commissioner for Patents (referred to collectively herein as "the PTO") to deny Photocure's application for a patent term extension ("PTE") for its U.S. Patent No. 6,034,267 ("the '267 patent") (A635-43[1]) because that decision is contrary to the plain language of the statute (35 U.S.C. § 156) providing for patent term extensions and binding precedent from this Court and the Federal Circuit construing that statute.

The patent term extension statute was enacted in part to compensate patentees for patent term lost to time spent obtaining marketing approval for a patented drug product. The statute requires in part that, to be eligible for an extension, a product's approval must represent "the first permitted commercial marketing or use of the product under the provision of law under which such regulatory review period occurred." 35 U.S.C. § 156(a)(5)(A). The statute defines "product" to mean "drug product," and defines "drug product" to mean "the active ingredient of a new drug...including any salt or ester of the active ingredient."

Photocure sought to extend the term of the '267 patent based on the approximately 4½-year period for it to obtain approval for its Metvixia™ drug product from the U.S. Food and Drug Administration ("FDA"). The claims of the '267 patent cover the Metvixia™ drug product and the approved method of using this product.[2] (A353-A357, A409.) The PTO found

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[1] References to "A" followed by a number refer to pages of the Certified Copy of the Administrative Record filed with the Court by Defendants. *See* Docket Entry 9.

[2] The Metvixia™ drug product is used to treat skin diseases. The product is a cream that is applied to the skin. A chemical substance present in the cream then passes through the skin and concentrates in cells to be treated. These cells convert the substance into an excess amount of a (continued…)

that the Metvixia™ drug product was not "the first permitted commercial marketing or use of the product," but rather that the previously-approved Levulan® drug product was the first such approved product. However, the PTO has admitted that the active ingredient in the Metvixia™ drug product is methylaminolevulinate hydrochloride ("MAL HCl"), and that the Levulan® drug product does not contain this same active ingredient or a salt or ester of this active ingredient. Specifically, the Levulan® drug product contains aminolevulinic acid hydrochloride ("ALA HCl") as its active ingredient, which is not the same as MAL HCl, nor is it a salt or ester of MAL HCl. Thus, Photocure's PTE request should have been granted.

The PTO gave two separate bases for its denial of Photocure's PTE request. The PTO initially rejected Photocure's PTE request on the grounds that the approval of the Metvixia™ drug product did not represent the first permitted commercial marketing or use of "the product," as required by the statute, because MAL HCl is an ester of ALA HCl, and ALA HCl had previously been approved. (A412-A413.) After Photocure submitted a request for reconsideration pointing out that ALA HCl is not the same as, nor a salt or ester of, MAL HCl (A415-20), the PTO apparently abandoned that theory, and instead held that MAL HCl and ALA HCl are the same "product," as that term is defined in the statute, because they share the same "active moiety" or "underlying molecule." Notably, neither of these terms appear anywhere in the statute. According to the PTO, the term "active ingredient" does not refer to a substance that is actually in the drug product, even though that is the plain meaning of the word "ingredient". Rather, it refers to a "form" of the actual active ingredient with any salt ions or ester groups

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naturally-occurring, light-sensitive compound. Light is then shown on the skin, which activates the compound, resulting in a chemical chain reaction that ultimately kills the cells to be treated. The elimination of cells by activation of a light-sensitive substance is referred to as "photodynamic therapy."

removed[3] – which the PTO refers to as the "active moiety" or the "underlying molecule" – regardless of whether that form is actually present in the drug product at issue, and despite the complete absence from the statute of those terms or any other indication that "active ingredient" should be construed contrary to its plain meaning. (A637-41.)

The PTO's decision should be held unlawful and set aside under 35 U.S.C. § 706 because both of the bases that it has given for its decision are contrary to the statute. First, according to the plain language of the statute, the proper analysis is whether the active ingredient of the Metvixia™ drug product or a salt or ester of that active ingredient, was previously approved, ***not*** whether the active ingredient of the Metvixia™ drug product is a salt or ester of a previously-approved product. Thus, the PTO's initial rationale for denying Photocure's PTE request is contrary to the statute. Second, as this Court and the Federal Circuit have specifically held, the plain language of the statute shows that the term "active ingredient" should not be construed to mean "active moiety." *See Glaxo Operations UK Ltd. v. Quigg*, 706 F. Supp. 1224 (E.D. Va. 1989) ("*Glaxo I*"), *aff'd.*, 894 F.2d 392 (Fed. Cir. 1990) ("*Glaxo II*"). Thus, the PTO's later rationale for denying Photocure's PTE request is also contrary to the statute. Accordingly, since all of the other requirements for an extension are indisputably satisfied, Photocure respectfully requests that the Court declare that Photocure's application satisfies the requirements of 35 U.S.C. § 156, and compel the PTO to take appropriate action to extend the term of the '267 patent in accordance with the provisions of the statute.

## PROCEDURAL STATUS

On September 19, 2008, the parties submitted an Agreed Order to the Court indicating that the parties agree that discovery is not necessary, and that the matter can be decided on cross-

[3] The PTO also refers to this as "a non-salified and non-esterified form of a molecule." (A637.)

motions for summary judgment. (Docket Entry 10.) The parties further agreed on a briefing schedule. (*Id.*) This is Photocure's opening brief in support of its summary judgment motion. The parties have agreed to notice their cross-motions for hearing on December 5, 2008. (*Id.*)

## LIST OF UNDISPUTED MATERIAL FACTS

1. On July 27, 2004, the FDA approved NDA No. 21-415 for Photocure's Metvixia™ drug product. (A635.)

2. On September 22, 2004, Photocure timely filed with the PTO an application for extension of its U.S. Patent No. 6,034,267 pursuant to 35 U.S.C. § 156. (A351-A408, A635.) The request for extension was based on the regulatory review period for Photocure's Metvixia™ drug product. (A353.)

3. The '267 patent had not expired prior to the application for extension. (A359.)

4. The '267 patent has never been extended under 35 U.S.C. § 156. (A359.)

5. In accordance with standard procedure, upon receiving Photocure's PTE request, the PTO first communicated with FDA about the approval of the Metvixia™ drug product in a letter dated approximately November 7, 2006. (A409-10.) In response to the PTO's communication, FDA responded on approximately March 5, 2007 that the Metvixia™ drug product was not the first approval of the active ingredient in that product because the active ingredient in that product – methylaminolevulinate hydrochloride (MAL HCl) – is an ester of aminolevulinic acid hydrochloride (ALA HCl), the active ingredient in the Levulan® drug product, which had been previously approved:

> The active ingredient in Metvixia, methylaminolevulinate hydrochloride, is an ester of aminolevulinic acid hydrochloride, an active ingredient that has been previously approved for commercial marketing or use as Levulan, NDA 20-965.

(A411.)

6. On approximately April 11, 2007, the PTO dismissed the application for patent term extension in a Notice of Final Determination-Ineligible. (A412-14.) In so doing, the PTO – like FDA – stated that the Metvixia™ drug product was not the first approval of the active ingredient in that product because the active ingredient in that product – MAL HCl – is an ester of ALA HCl, the active ingredient in the Levulan® drug product, which had been previously approved:

> 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.

(A413.)

7. On approximately November 9, 2007, Photocure timely filed a Request for Reconsideration of the Final Determination. (A415.)

8. On approximately May 13, 2008, the PTO denied the request for reconsideration. (A635.) In so doing, the PTO did not rely on the basis that it had previously relied upon to reject Photocure's PTE request – namely, that the Metvixia™ drug product was not the first approval of the active ingredient in that product because the active ingredient in that product –MAL HCl – is an ester of ALA HCl, the active ingredient in the Levulan® drug product, which had been previously approved. Instead, the PTO held that the active ingredient in a drug product is the "active moiety" or "underlying molecule" in that drug product, and that the active ingredient in both the Metvixia™ and Levulan® drug products is aminolevulinic acid ("ALA"). (A637-41.)

9. The FDA approved NDA 20-965 for the Levulan® drug product before it approved the Metvixia™ drug product. (A412, A637.)

10. The PTO has stated that the active ingredient of Levulan® is ALA HCl. (A413, A636.) The FDA's Electronic Orange Book indicates that the active ingredient in the Levulan® drug

product is ALA HCl. (Ex. 1[4].)

11. The PTO has stated that the active ingredient of the Metvixia™ drug product is MAL HCl. (A413, A636.) The FDA's Electronic Orange Book indicates that the active ingredient in the Metvixia™ drug product is MAL HCl. (Ex. 2.) The FDA-approved prescribing information for the Metvixia™ drug product indicates that the active ingredient in that drug product is MAL HCl. (Ex. 3 at 018.)

12. Methylaminolevulinate hydrochloride is an ester of aminolevulinic acid hydrochloride. (A413.)

13. Aminolevulinic acid hydrochloride is not the same as or a salt or an ester of methylaminolevulinate hydrochloride. (A641.)[5]

14. Claims 1 and 3-7 of the '267 patent encompass methods of diagnosing or treating including the approved method of using the Metvixia™ drug product to treat "non-hyperkeratotic actinic keratoses" of the face and scalp. (A354-A356.)

15. Claims 8 and 9 of the '267 patent encompass compositions including the Metvixia™ drug product. (A356.)

16. An organic acid comprises either hydrogen or an organic chemical group R covalently bonded to an acid group COOH (representing a carbon atom covalently bound to two oxygen atoms, one of which is bound to a hydrogen atom), represented as RCOOH.

17. An ester of an organic acid comprises RCOOR', where R' represents a second organic chemical group bound to one of the oxygen atoms instead of the hydrogen of the organic acid.

18. An hydrochloride salt of an organic compound comprises an organic compound to which

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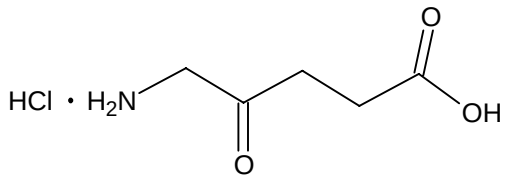
[4] The exhibits submitted with this brief are attached to the Declaration of Erik C. Kane, submitted herewith, and cited herein as "Ex. __."

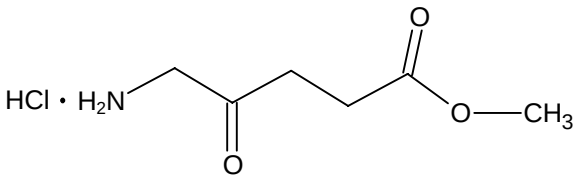
[5] Facts 12 and 13 are illustrated by Facts 18 and 19 below.

a hydrogen atom has been donated by hydrochloric acid (HCl). The resulting, "protonated" molecule has a positive charge, and is joined by an ionic bond to the remaining negatively charged ion of the acid. For example, the hydrochloride salt of methyl aminolevulinate ($CH_3OC(O)(CH_2)_2C(O)CH_2NH_2$) would be $CH_3OC(O)(CH_2)_2C(O)CH_2\underline{NH_3^+Cl^-}$ (also written as $CH_3OC(O)(CH_2)_2C(O)CH_2NH_2$•HCl). This is MAL HCl.

19. The chemical structures of aminolevulinic acid hydrochloride and methylaminolevulinate hydrochloride are shown below.




ALA hydrochloride




methyl aminolevulinate hydrochloride

A418.

20. Aminolevulinic acid is an organic acid. Aminolevulinic acid hydrochloride is the hydrochloride salt of aminolevulinic acid. Methylaminolevulinate hydrochloride is an ester of aminolevulinic acid hydrochloride. Specifically, in methylaminolevulinate hydrochloride, the -H from the -COOH group in aminolevulinic acid hydrochloride is replaced by a $–CH_3$ group (known as a "methyl" group). Thus, methylaminolevulinate hydrochloride is the "methyl ester" of aminolevulinic acid hydrochloride.

## ARGUMENT

### I. Legal Standards

#### A. Standard of Review

This case calls for judicial review of a final agency decision. (A642.) The Administrative Procedure Act ("APA") therefore provides the applicable standard of review.

*See Glaxo I*, 706 F. Supp. at 1233 n.20; *Glaxo II*, 894 F.2d at 394 n.4. Under the APA, agency action may be set aside if, upon reviewing the administrative record, the court finds that the agency action is "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law," "contrary to constitutional right, power, privilege, or immunity," "in excess of statutory jurisdiction, authority, or limitations, or short of statutory right," or "without observance of procedure required by law." 5 U.S.C. §§ 706(2)(A)-(D); *Tafas v. Dudas*, 541 F. Supp. 2d 805, 810-11 (E.D. Va. 2008). Moreover, "it is well established that an agency's action must be upheld, if at all, on the basis articulated by the agency itself." *See Glaxo I*, 706 F. Supp. at 1226 n.5 (*quoting Motor Vehicle Manufacturer's Ass'n v. State Farm Mutual Automobile Ins. Co*., 463 U.S. 29, 50, 77 L. Ed. 2d 443, 103 S. Ct. 2856 (1983) (citations omitted)).

**B. Summary Judgment**

Summary judgment is appropriate where it is shown that there is no genuine issue as to any material fact and that the movant is entitled to judgment as a matter of law. Fed. R. Civ. P. 56(c); *see Tafas*, 541 F. Supp. at 810. Here, the parties agree that this case is amenable to resolution on summary judgment. (Docket Entry 10.)

**C. Patent Term Extension Under 35 U.S.C. § 156**

Under 35 U.S.C. § 156, the term of a patent "shall be extended" when the patent claims a product that has been approved for commercial marketing or use and certain other conditions also are met. *See* 35 U.S.C. § 156. These other conditions are 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.

35 U.S.C. § 156 (emphasis added).

The statute further defines "product" as follows:

(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)…including any salt or ester of the active ingredient, as a single entity or in combination with another active ingredient."
>
> *Id.* (emphasis added).

*Id.* (emphasis added).

## II. Under the Plain Language of the Statute and Applicable Judicial Precedent, Photocure's PTE Request Should Have Been Granted

Under the statute, to determine whether the permission to market Photocure's Metvixia™ drug product constitutes the "first permitted commercial marketing or use of the product," one must first determine what the relevant "product" is, and then second determine whether that product had been previously approved.

### A. The Relevant "Product" Here Is MAL HCl, and Any Salt or Ester of MAL HCl

The term "product" is defined as "drug product," which in turn is defined as "the active ingredient of. . . a new drug. . . including any salt or ester of the active ingredient." Thus, to determine what the relevant "product" is, one must determine what the "active ingredient" is in Photocure's Metvixia™ drug product. *See* 35 U.S.C. § 156(f)(2).

The term "active ingredient" is not defined in the statute. However, that term has a plain meaning, which is "a constituent element of a mixture that provides a therapeutic effect when administered to a patient." This is because an "ingredient" is "a constituent element of a mixture or compounds," *see Glaxo I,* 706 F. Supp. at 1227, while an "active" ingredient is one that "provides a therapeutic effect." *See* Hawley's Condensed Chemical Dictionary[6] 23 (Richard J. Lewis, Sr. ed., 15th ed. 2007) (defining active pharmaceutical ingredient" as "[t]he biologically active compound in a drug formulation that imparts the desired therapeutic effect.") (Ex. 7.) In

[6] *See Glaxo II*, 894 F.2d at 393 n.2 (citing the Hawley chemical dictionary with approval).

other words, an active ingredient is a substance that can be found in a mixture, not just something that can be derived from a mixture or from which an ingredient in the mixture can be derived. *See Glaxo I*, 706 F. Supp. at 1227; *see also Hoechst-Roussel Pharms. Inc. v. Lehman*, 109 F.3d 756, 759 n.3 (Fed. Cir. 1997) (finding that a metabolite produced when a drug product was administered was not an "active ingredient" because "[f]or purposes of patent term extension, this active ingredient must be present in the drug product when administered.")

In *Glaxo I*, this Court considered what the "active ingredient" was in a drug product referred to as Ceftin Tablets. The tablets actually contained the compound "cefuroxime axetil," which was an ester of the organic acid "cefuroxime." However, the PTO argued that the "active ingredient" in Ceftin Tablets was cefuroxime instead of cefuroxime axetil because cefuroxime could be derived from cefuroxime axetil. This Court rejected this argument because cefuroxime was not one of the "ingredients" of the Ceftin Tablets, stating:

> It is cefuroxime axetil that is the "active ingredient" in Ceftin Tablets. Cefuroxime itself is not present at all in Ceftin Tablets; it is therefore not an "ingredient." This conclusion is inescapable given the plain and unambiguous language of the statute. An ingredient is a "constituent element of a mixture or compounds." *Webster's Second University Dictionary* (1984). It must be something found in the mixture or compound, not just something that can be derived from it or from which the mixture or compound can be derived. Simply because the ester cefuroxime axetil may be derived from the acid cefuroxime through esterification is no basis for concluding that cefuroxime is some how an "ingredient." One might as well say that a caterpillar is an ingredient of a butterfly. This is palpably not so. ***To be sure, a butterfly comes from, or derives from, a caterpillar in metamorphosis as does the ester from the acid in esterification. But there is no caterpillar that is part of a butterfly, just as the acid itself is not a part of or found in the ester.***

*Id.* at 1227-28 (footnote omitted, emphasis added).

Thus, even though the Ceftin Tablets contained cefuroxime axetil – which is an ester of the organic acid cefuroxime – this Court held that cefuroxime was not an "ingredient" – and therefore not an "active ingredient" – of the Ceftin Tablets. In other words, the organic acid was

not somehow found in the ester. Indeed, this Court held that this was the "plain and unambiguous language of the statute." *Id.* at 1227. This Court further held that the legislative history did not provide a basis for disregarding this plain and ordinary meaning. *Id.* at 1228; *see also Glaxo II*, 894 F.2d at 396-98.[7] Finally, the Court rejected the PTO's argument that cefuroxime should be considered the "active ingredient" in the Ceftin tablets because it was the "active moiety" in those tablets. 706 F. Supp. at 1228 ("Equating 'active moiety' with 'active ingredient,' as the Commissioner urges, results in reading out of the statute the plain meaning of the phrase Congress chose. This is unwarranted. . .".)

In holding that cefuroxime axetil was the "active ingredient" in Ceftin Tablets, this Court relied on the following pieces of evidence: (i) the PTO's previous statements that cefuroxime axetil was the active ingredient in the Ceftin Tablets, (ii) the FDA-approved labeling for the Ceftin Tablets, which indicated that cefuroxime axetil was the active ingredient in those tablets, and (iii) the FDA's Orange Book listing for the Ceftin Tablets, which indicated that cefuroxime axetil was the active ingredient in the Ceftin Tablets. *Id.* at 1228 n.7. This Court's decision was affirmed on appeal by the Federal Circuit. *See Glaxo II*, 894 F.2d 392-93 (affirming because "the district court correctly construed and properly applied the operative terms of the Act").

Here, for exactly the same reasons as this Court relied upon in *Glaxo I*, the active ingredient in the Metvixia™ drug product is MAL HCl, and not ALA. For one thing, MAL HCl is indisputably the active ingredient in the Metvixia™ drug product. While the PTO appears to contend that ALA is the active ingredient in the Metvixia™ drug product because MAL HCl is

[7] When "the terms of a statute [are] unambiguous, judicial inquiry is complete, except in rare and exceptional circumstances." *Glaxo II*, 894 F.2d at 395 (quoting *United States v. James*, 478 U.S. 597 (1986)). "If the statutory language is unambiguous, in the absence of 'a clearly expressed legislative intent to the contrary, that language must ordinarily be regarded as conclusive.'" *Glaxo I*, 706 F. Supp. at 1229 (quoting *United States v. Turkette*, 452 U.S. 576, 580 (1981)).

an ester of ALA HCl and is thereby derived from ALA HCl (A637), this Court squarely rejected this contention in *Glaxo I*, 706 F. Supp. at 1228 ("To be sure, a butterfly comes from, or derives from, a caterpillar in metamorphosis as does the ester from the acid in esterification. But there is no caterpillar that is part of a butterfly, just as the acid itself is not a part of or found in the ester.")

Moreover, as in *Glaxo I*, the PTO has on several occasions stated that the active ingredient in the Metvixia™ drug product is MAL HCl. *See* A413 ("The active ingredient in the approved product METVIXIA™ is methyl aminolevulinate hydrochloride."); *see also* A412 "Extension is sought based upon the premarket review. . . of a human drug product known by the tradename METVIXIA™ having the active ingredient methyl aminolevulinate hydrochloride."[8] Further, just as in *Glaxo I*, the FDA-approved labeling for the Metvixia™ drug product identifies MAL HCl – not ALA – as the active ingredient: **"What are the ingredients in Metvixia Cream?** Active ingredient: methyl aminolevulinate hydrochloride." (Ex. 3 at 018.) Finally, just as in *Glaxo I*, the Orange-Book listing for the Metvixia™ drug product identifies MAL HCl – not ALA – as the active ingredient. (Ex. 2.)

For all of these reasons, under the plain language of the statute and binding precedent from this Court and the Federal Circuit, the "active ingredient" in the Metvixia™ drug product is MAL HCl. Accordingly, the relevant "product" here is MAL HCl (*i.e.*, the "active ingredient"), and any salt or ester of MAL HCl.

[8] Photocure notes that the FDA likewise referred to "[t]he active ingredient in Metvixia" as "methylaminolevulinate hydrochloride" when considering Photocure's PTE request. (A411.)

### B. Neither MAL HCl Nor a Salt or Ester of MAL HCl Had Been Approved Before the Approval of the Metvixia™ Drug Product

Under the statute, the second inquiry is whether the relevant "product" had been previously approved. As explained above, the relevant product here is MAL HCl, and any salt or ester of MAL HCl. Before the Metvixia™ drug product was approved by FDA, it is undisputed that neither MAL HCl or a salt or ester of MAL HCl had been approved. (A641.) In particular, the Levulan® drug product does not contain MAL HCl or a salt or ester of MAL HCl, as ALA is not MAL HCl nor a salt or ester of MAL HCl. Thus, the approval of the Metvixia™ drug product represents the first permitted commercial marketing or use of MAL HCl or a salt or ester of MAL HCl. Since Photocure's PTE request satisfied all of the other statutory requirements (notably, the PTO has not cited any requirements that are not satisfied other than the "first permitted commercial marketing" of § 156(a)(5)), that request should have been granted.[9]

In much the same way, in *Glaxo I*, this Court held that the approval of the Ceftin Tablets – which contain cefuroxime axetil as the active ingredient – could be relied upon to support a PTE request even though cefuroxime salts had been previously approved. This was because cefuroxime salts were not the same as cefuroxime axetil, nor were they salts or esters of cefuroxime axetil. *Id.* at 1232 ("Further, it is undisputed that no prior FDA approval exists for cefuroxime axetil, or any ester or acid of it. From this, it follows that (a)(5)(A) is satisfied and that the Commissioner's contrary decision is arbitrary and capricious."). Again, this decision was affirmed by the Federal Circuit. *See Glaxo II*, 894 F.2d 392.

[9] At various times, the PTO has appeared to take the position that the relevant inquiry is whether MAL HCl is a salt or ester of ALA or ALA HCl, as opposed to whether ALA or ALA HCl is a salt or ester of MAL HCl. This contention is addressed in Argument Section IV. below.

## III. The PTO's Final Decision Denying Photocure's PTE Request Should Be Set Aside Because It Was Based on an Erroneous Construction of the Term "Active Ingredient" in 35 U.S.C. § 156 and Thus Was Arbitrary, Capricious, and Not in Accordance With Law

### A. The PTO's Final Decision Is Not Supported By the Plain Language of the Statute

In its Final Decision denying Photocure's PTE request, after quoting the relevant portions of the statute (which are quoted above in Argument Section I.C.), the PTO stated as follows in holding that the "plain language" of the statute shows that Photocure's PTE request should be denied:

> Hence, by the explicit terms of the 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."

(A637.)

In so doing, the PTO construed the term "active ingredient" to mean "a non-salified and non-esterified form of a molecule." Contrary to the PTO's assertion, this construction is not supported by the plain language of the statute. The PTO's construction does not require the "active ingredient" to be a substance actually found in the drug product, but rather seems to require that it be "a non-salified and non-esterified form" of a substance found in the drug product (*i.e.*, a modified form of a substance found in a drug product in which any salt or ester portions have been removed). This is contrary to the plain meaning of the word "ingredient." *See Glaxo I*, 706 F. Supp. at 1227-28.

Congress could have clearly articulated definitions of "product" and "active ingredient" that accord with the PTO's construction. The fact that Congress did not do so indicates that the PTO's construction is inconsistent with and contrary to the statute's true meaning. For example, Congress could have defined, but did not define, "active ingredient" to mean "either the active

ingredient if the active ingredient is not a salt and/or an ester, or, if the active ingredient is a salt and/or ester, the non-salt and/or non-ester form of the active ingredient." *See Glaxo II*, 894 F.2d at 397 ("Congress chose particular terms--'active ingredient,…including any salt or ester of an active ingredient….' Accordingly, we can infer that in so choosing, Congress may have deliberately rejected the very terms the Commissioner asserts were the intended meaning of section 156.").

There are other serious problems with the PTO's proposed construction.

For one thing, under the PTO's proposed construction, the active ingredient in the Ceftin Tablets would be cefuroxime, since that is the "non-salified and non-esterified form of" cefuroxime axetil (*i.e.*, cefuroxime is a modified form of cefuroxime axetil in which the ester portion has been removed). But this is precisely the conclusion that this Court rejected in *Glaxo I* and the Federal Circuit rejected in *Glaxo II*. In addition, under the PTO's proposed construction, the active ingredient in Photocure's Metvixia™ drug product would be ALA, since that is the "non-salified and non-esterified form of" MAL HCl (*i.e.*, MAL HCl in which the methyl ester and HCL salt portions have been removed). But this is directly contrary to the previous statements of both the PTO and the FDA that the active ingredient in the Metvixia™ drug product is MAL HCl. *See* A413 ("The active ingredient in the approved product METVIXIA™ is methyl aminolevulinate hydrochloride."); *see also* A411, A412.

**B. The PTO's Final Decision Is Not Supported By Judicial Precedent**

In denying Photocure's PTE request, the PTO stated that judicial precedent supported its position. (A638-41.) In particular, the PTO took the position that judicial precedent indicated that the term "active ingredient," as used in 35 U.S.C. § 156, should be interpreted to mean "active moiety," relying on *Fisons v. Quigg*, *Pfizer v. Ranbaxy*, and 21 C.F.R. § 60.3(b)(2). As explained below, none of these authorities support the PTO's position. Rather, judicial precedent

solidly supports Photocure's position.

### 1. *Fisons v. Quigg* Does Not Support the PTO's Final Decision

The PTO's Final Decision misplaces reliance on *Fisons v. Quigg*, 1988 U.S. Dist. LEXIS 10935 (D.D.C. 1988) ("*Fisons I*") (Ex. 4), *aff'd*, 876 F.2d 99 (Fed. Cir. 1989) ("*Fisons II*"). (A638-A639.) In *Fisons I*, applicants obtained approval for a formulation that contained an active ingredient (cromolyn sodium), and subsequently applied for patent term extensions based on the subsequent approval of different formulations containing, and a different indication using, the identical active ingredient (cromolyn sodium). *See Fisons I*, 1988 U.S. Dist. LEXIS at *3-8 (Ex. 4). In other words, the difference between the earlier-approved formulation and the later-approved formulation was that they contained different ***in***active ingredients and/or that they were approved to treat different conditions (*i.e.*, different "indications"), and not that they contained different active ingredients. The court held that no extension based on approval of the later-approved formulations or indications could be obtained because they were not the first permitted commercial marketing or use of the "product," meaning the active ingredient. *See id.* at *1-8, 13-16, and 32-35. The Federal Circuit affirmed the district court's construction of "product" as used in section 156(a)(5)(A). *See Fisons II*, 876 F.2d at 102. This holding is inapposite here, as the products at issue in this case do not contain the identical active ingredient but different inactive ingredients. Rather, they contain different active ingredients, as well as different inactive ingredients.

The PTO's Final Decision points to the fact that the *Fisons I* court considered parts of the legislative history of section 156 and concluded that "Congress's intent was to restore patent life only to new chemical entities." (A638.) However, contrary to the PTO's suggestions, the *Fisons I* court never suggested or stated that an active ingredient is or should be construed to refer to a

"new chemical entity" or to an "active moiety." *See Fisons I*, 1988 U.S. Dist. LEXIS at *14-15 (Ex. 4). Thus, the *Fisons I* court did not reach the result that the PTO is arguing for here. Moreover, in *Glaxo II*, the Federal Circuit flatly rejected the PTO's contention that the legislative history indicates that "active ingredient" should be construed to mean "active moiety." The *Glaxo II* court could not find in the legislative history "any clear statement that extensions are required based on first approval of 'new chemical entities.'" *See Glaxo II*, 894 F.2d at 398. Notably, the *Glaxo II* Court specifically considered and rejected the exact same legislative history that is cited in the *Fisons I* opinion, and that the PTO relies on here. *See id.* at 398; A638. In sum, the Federal Circuit has considered section 156's legislative history and found that it does not support construing the statutory terms at issue contrary to their ordinary meaning.

**2. *Pfizer v. Dr. Reddy's* Does Not Support the PTO's Final Decision**

**a. *Pfizer v. Dr. Reddy's* Dealt With the Issue of the Scope of a PTE During the Extended Term, and Not With the Issue of Whether a PTE Request Involved a Product That Had Not Been Previously Approved**

The PTO's Final Decision also improperly relies on *Pfizer Inc. v. Dr. Reddy's Labs., Ltd.*, 359 F.3d 1361 (Fed. Cir. 2004) ("*Pfizer II*").[10] (A639-A640.) In *Pfizer II*, the Court addressed the scope of the rights to which a patent owner was entitled during the extended term of a PTE. The statute provides that "the rights derived from any patent the term of which is extended under this section shall during the period during which the term of the patent is extended. . . in the case of a patent which claims a product, be limited to any uses approved for the product." 35 U.S.C. § 156(b). Pfizer's patent claimed amlodipine. It had obtained a patent term extension for that

[10] The Federal Circuit in *Pfizer* reversed the district court's decision. We will refer to the district court's decision, *Pfizer Inc. v. Dr. Reddy's Labs., Ltd.*, 2002 Extra LEXIS 610 (D.N.J. Dec. 17, 2002) (Ex. 5), as "*Pfizer I*" and the Federal Circuit's decision, *Pfizer Inc. v. Dr. Reddy's Labs., Ltd.*, 359 F.3d 1361 (Fed. Cir. 2004), as "*Pfizer II*."

patent based on the time it took to get approval for its Norvasc® drug product, which contained the besylate salt of amlodipine. The Dr. Reddy's product contained a different salt of amlodipine. The issue before the Court was whether Pfizer's patent covered the Dr. Reddy's product during its extended term, or whether that patent instead only covered the approved drug product – the besylate salt of amlodipine – during the extended term.

In *Pfizer I*, the district court, relying heavily on *Glaxo II*, held that, during the extended term, Pfizer's patent only covered the approved product, and that this product was the besylate salt of amlodipine. The Federal Circuit reversed, holding (in a 2-1 decision involving a dissent by Chief Judge Mayer) that the scope of the patent during its extended term encompassed not only the approved product, amlodipine besylate, but also amlodipine maleate. *See Pfizer II*, 359 F.3d at 1366. The Court stated that "the active ingredient is amlodipine, and that it is the same whether administered as the besylate salt or the maleate salt," and that the "[t]he statutory definition of 'drug product' is met by amlodipine and its salts." *Id.* at 1366. Although not entirely clear, one could argue that the basis of the Federal Circuit's decision was that the rights provided during the extended term were limited to the approved product, but that the approved product included amlodipine and all its salts because those all have the same active ingredient – namely, amlodipine.[11] The Federal Circuit did not allude to or attempt to reconcile its decision

[11] However, one could also argue that the Federal Circuit in *Pfizer II* simply determined that 35 U.S.C. § 156(b), which sets forth the rights that a PTE confers during the extended period, limits those rights to the ***approved uses*** of the drug product relied upon to support the extension, but does not limit those rights to the active ingredient in that drug product. *See Pfizer II*, 359 F.3d at 1366 ("The 'rights derived' provision of *§ 156(b)* specifically limits the extension to 'any use approved for the product,' which means that other, e.g., non-pharmaceutical uses, are not subject to the extension. ***That provision does not contain any limitation regarding the form of the product subject to the extension***.") (emphasis added). Thus, under this view, the rights conferred during the extended term were not limited to amlodipine besylate because there is no statutory basis for limiting those rights to the approved drug product (rather, the only limitation is to the approved uses).

with its earlier decision in *Glaxo II*.

*Pfizer II* is best understood as defining, under section 156(b), the rights of a patentee during the period that the patent is extended, which are not at issue in this case. According to this understanding, *Pfizer II* is not relevant to the issue at hand,[12] which is whether, under section 156(a), the '267 patent should be extended. Rather, the leading cases are *Glaxo I* and *Glaxo II*, which require that an extension be granted. As discussed above, *Glaxo II* addressed the issue of whether an extension should be granted based on the approval of a product containing an ester of cefuroxime (cefuroxime axetil) when products containing salts of cefuroxime had previously been approved. This Court held, and the Federal Circuit affirmed, that an extension was warranted because the salts were neither salts nor esters of the ester at issue, construing the statutory term "product" (according to its explicit definition in the statute) to refer to the active ingredient present in the approved product, and not the "active moiety" of the active ingredient.

**b. Assuming *Arguendo* That *Pfizer II* Is Inconsistent With *Glaxo II*, Then *Glaxo II* Controls Because It Was Decided Earlier in Time**

However, if *Pfizer II* is understood to construe the statutory term "product," as defined in section 156(f) and used throughout the statute, to refer to the "active moiety" or "underlying molecule," then *Pfizer II* must be viewed as being in conflict with *Glaxo II*. When two Federal Circuit decisions conflict, the earlier decision, in this case *Glaxo II*, is binding. *See Texas Instruments Inc. v. Cypress Semiconductor Corp.*, 90 F.3d 1558, 1567 (Fed. Cir. 1996), *Newell Cos., Inc. v. Kenney Mfg. Co.*, 864 F.2d 757, 765 (Fed. Cir. 1988) ("This court has adopted the

[12] The irrelevance of *Pfizer II* to the issues at hand is shown by the fact that the case was not cited in the PTO's original letter to FDA indicating that the approval of Metvixia did not represent the first approval of the active ingredient in that product (A409-10), FDA's response to that letter (A411), the PTO's initial decision denying Photocure's PTE request (A412-14), or Photocure's request for reconsideration. (A415-20.)

rule that prior decisions of a panel of the court are binding precedent on subsequent panels unless and until overturned *in banc*. Where there is direct conflict, the precedential decision is the first [internal citations omitted].”). Thus, in these circumstances, *Glaxo II* should be followed.

**3. FDA Regulations Do Not Support the PTO’s Final Decision**

The PTO cites the definition of “active ingredient” from 21 C.F.R. § 60.3 (b)(2) in support of its construction of 35 U.S.C. § 156. (A640.) As an initial matter, it should be noted that, contrary to the PTO’s assertions (A640), this regulation does not define “active ingredient” to mean “active moiety” (it never uses the phrase “active moiety”). More fundamentally, in *Glaxo II*, *the* Federal Circuit specifically found that the FDA’s interpretation of the term “active ingredient” was not persuasive and was not entitled to deference. *See Glaxo II*, 894 F.2d at 399 n.11. In so holding, the Court stated as follows: “First, the FDA's interpretation, like the Patent and Trademark Office's, may be based on its own judgment of what is better policy. Second, the FDA’s interpretation of plain statutory terms is as unlikely to require technical expertise and technical judgment as is the [PTO] Commissioner's.” *Id.* The Court thus concluded that it was not obligated to defer to the FDA’s interpretation. *See id.* at 399-400. Likewise, this Court should not defer to the FDA’s interpretation of “active ingredient” in deciding this case.

**4. The PTO’s Attempt to Distinguish *Glaxo II* Is Untenable**

Finally, the PTO argues that the Federal Circuit’s decision in *Glaxo II* is not on point here because the meaning of “active ingredient” was not at issue in that case. (A640.) This is nonsense. As explained above, in *Glaxo I*, this Court construed the term “active ingredient,”[13] and specifically rejected the PTO’s argument that “active ingredient” means “active moiety.”

[13] Indeed, this Court stated that “[t]he central question then is whether the active ingredient of Ceftin Tablets is the ester cefuroxime axetil or the parent acid cefuroxime.” 706 F. Supp. at 1227.

706 F. Supp. at 1228 ("Equating 'active moiety' with 'active ingredient,' as the Commissioner urges, results in reading out of the statute the plain meaning of the phrase Congress chose. This is unwarranted. . .".) This Court's construction of that term was reviewed and affirmed on appeal by the Federal Circuit in *Glaxo II*. 894 F.2d at 392-93. The PTO's additional contention that the Federal Circuit's determination in *Glaxo II* focused on the definition of the term "product, and not the term "active ingredient" (A640), also misses the mark because the term "product" is defined in the statute as "active ingredient" (*i.e.*, if "product" is synonymous with "active ingredient" and "product" does not mean "active moiety," then "active ingredient" does not mean "active moiety" either). Indeed, the PTO's current position that *Glaxo II* did not address the meaning of "active ingredient" (and that *Glaxo II* and *Pfizer II* are thus consistent with one another) is belied by the position the PTO took in denying a 2005 request for a patent term extension, wherein the PTO stated that "*Glaxo* must be treated as overruled" by *Pfizer II*. *See In re Patent Term Extension Application for U.S. Patent No. 6,143,771*, 2005 Commr. Pat. LEXIS 15 (July 28, 2005) (Ex. 6). If the PTO thinks *Pfizer II* overruled *Glaxo II*, then surely it must believe that they address the same issue.

## IV. The PTO's Initial Decision Denying Photocure's PTE Request Should Be Set Aside Because It Was Based on an Erroneous Methodology for Determining Whether a Product Had Been Previously Approved and Thus Was Arbitrary, Capricious, and Not in Accordance With Law

The PTO initially rejected Photocure's PTE request because MAL HCl – which it referred to as the active ingredient in Photocure's Metvixia™ drug product – is an ester of ALA HCl – which it referred to as the active ingredient in the Levulan® drug product. (A413.) It is not clear whether the PTO continues to adhere to this initial position. The PTO did not rely on this initial position in its Final Decision, although it repeated it as part of repeating the procedural background. (A636.) Moreover, this initial position is inconsistent with the PTO's

position in the Final Decision, in that the initial position specifically acknowledges that MAL HCl is the active ingredient of the Metvixia™ drug product and that ALA HCl is the active ingredient in the Levulan® drug product, while the PTO now takes the position that ALA is the active ingredient in both drug products in the Final Decision. In any event, because the PTO has not formally retracted this position, Photocure will briefly address it here.

In holding that MAL HCl was the same product as ALA HCl because MAL HCl is an ester of ALA HCl, the PTO erred by inverting the analysis to be performed according to the statute in order to determine 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." 35 U.S.C. § 156(a)(5)(A). The term "product" refers to "the active ingredient of. . . a new drug. . . "including any salt or ester of the active ingredient." 35 U.S.C. § 156(f). Thus, under the statute, one must first determine the active ingredient in the drug product being relied upon to support the PTE request, and then one must determine whether that active ingredient, or a salt or ester of the that active ingredient, were previously approved.

This Court applied the statute in exactly this way in *Glaxo I* in evaluating whether the active ingredient in Ceftin Tablets – cefuroxime axetil – had been previously approved:

> In summary, it is undisputed that cefuroxime axetil is the active ingredient of Ceftin Tablets, not cefuroxime, which is not present at all in the tablets. ***Further, it is undisputed that no prior FDA approval exists for cefuroxime axetil, or any ester or acid of it. From this, it follows that (a)(5)(A) is satisfied and that the Commissioner's contrary decision is arbitrary and capricious.***

*Glaxo I*, 706 F. Supp. at 1232.

Notably, this Court did not look at whether cefuroxime axetil was the same as, or a salt or ester of, the cefuroxime salts that had been previously approved. Rather, this Court looked specifically at whether cefuroxime axetil or a salt or ester of cefuroxime axetil had been

previously approved.

Analogously, Photocure contends, and the PTO has acknowledged, that in this case, the active ingredient of the Metvixia™ drug product is MAL HCl. (A413.) Thus, under the statute, one must determine whether the marketing of MAL HCl (the "product"), or of any salt or ester of MAL HCl, had been approved prior to the approval of Metvixia™. The PTO acknowledged that there was no such prior approval. (A641.) It follows from the plain meaning of the statute, a meaning adopted by the Federal Circuit in parallel circumstances, that Photocure's '267 patent is eligible for extension on the basis of the approval of the Metvixia™ drug product containing MAL HCl as the active ingredient.

The PTO thus erred in denying Photocure's application for extension on the ground that MAL HCl is an ester of a previously-approved drug's active ingredient (ALA HCl of the Levulan® drug product). The correct analysis is whether ALA HCl is the same as, or a salt or ester of, MAL HCl. Clearly it is not. The PTO therefore should not have denied Photocure's application on the ground that the Levulan® drug product had been approved before the Metvixia™ drug product.

Under the plain reading, if an ester of a compound is approved after the compound is approved, the ester's approval provides a basis for patent term extension for the reasons set forth above. If, on the other hand, an ester of a compound is approved first, and later the compound itself is approved, the compound does not provide a basis for a patent term extension. Thus, the order of approvals determines whether one or two extensions can be granted under the statute. Although these "asymmetrical results" might at first seem strange, where the statutory language is clear and unambiguous, only Congress has the power to provide for an outcome different than that required by the statute. *See Glaxo*, 894 F.2d at 399-400. Further, there is a logical basis for

these results, in that developing a useful ester of a known compound for use as a drug may in fact be more difficult than developing the de-esterified form of an ester for use as a drug (*i.e.*, it may be more difficult to add an organic group to create an ester than to subtract one from an ester).

In *Glaxo I*, this Court noted that Congress might well have considered this basis in drafting the statute:

> Some may complain that giving the Act its plain meaning results in an unattractive asymmetry. The perceived asymmetry arises as follows: Giving "active ingredient" its plain, ordinary meaning results in granting patent term extensions where the new active ingredient is an ester, even though a salt or acid related to the ester were previously approved by FDA. Yet no extension is available where the active ingredient is an acid and a salt or ester of that acid has previously received FDA approval. Even if these results are asymmetrical, the short answer to this is that neither the Commissioner nor this Court sit to rewrite Congressional acts to ensure their symmetry. Congress has the widest latitude in deciding how to achieve its purposes. *Cf. Tennessee Valley Authority v. Hill, 437 U.S. 153, 194, 57 L. Ed. 2d 117, 98 S. Ct. 2279 (1978).* ***In any event, the asymmetry may be illusory because in general it is not exceptionally difficult to reach the acid form once the salt or ester has been isolated. By contrast, 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. Thus, there may be a sound basis for allowing the patent term extension in the one case, but not the other.***

*Glaxo I*, 706 F. Supp. at 1229 n.12.

In fact, the facts relating to the Metvixia™ drug producillustrate this point, since MAL HCl exhibits a number of significant advantages over ALA HCl, all of which help make MAL HCl patentable. (A419, A421-A427.) If MAL HCl had been the first approved drug, the use of ALA HCl would not have represented as significant an advance.

## V. Conclusion

For the reasons set forth above, Photocure respectfully requests that the Court grant its motion for summary judgment.

Respectfully submitted,

Date: October 14, 2008

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**CERTIFICATE OF SERVICE**

I hereby certify that, on the 14th day of October, 2008, I will electronically file the foregoing with the Clerk of Court using the CM/ECF system, which will then send a notification of such filing (NEF) to the following individual, and that I will also have the foregoing sent by e-mail to the following individual:

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