2009-1393

United States Court of Appeals
FOR THE FEDERAL CIRCUIT

PHOTOCURE ASA,

Plaintiff-Appellee,

v.

JOHN J. DOLL, Acting Under Secretary of Commerce for Intellectual Property and Acting Director of the United States Patent and Trademark Office,

Defendant-Appellant.

Appeal from the United States District Court for the Eastern District of Virginia in Case No. 1:08-CV-718, Judge Liam O'Grady

BRIEF FOR PLAINTIFF-APPELLEE PHOTOCURE ASA

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CERTIFICATE OF INTEREST

Counsel for Plaintiff-Appellee Photocure ASA certifies the following:

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

2. The name of the real party in interest represented by me is: Photocure ASA.

3. All parent corporations and any publicly held companies that own 10 percent or more of the stock of the party or amicus curiae represented by me are: none.

4. The names of all law firms and the partners or associates that appeared for the party or amicus now represented by me in the trial court or agency or are expected to appear in this court are: John W. Bateman, Richard L. DeLucia, Lawrence H. Frank and Erik C. Kane, all of Kenyon & Kenyon LLP.

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STATEMENT OF RELATED CASES

No other appeal in or from the present action was previously before this or any other appellate court. This Court's decision in this appeal may directly affect or may be directly affected by *Ortho-McNeil Pharmaceutical, Inc. et al. v. Lupin Pharmaceutical, Inc., et al.*, Fed. Cir. No. 2009-1362. Pursuant to an unopposed motion submitted by the PTO in this appeal, the oral argument in this appeal and the oral argument in the *Ortho-McNeil* appeal are currently scheduled to be heard on the same day in September and in front of the same panel.

STATEMENT OF THE ISSUES

1) Did the district court correctly hold that this Court's decision in *Glaxo Operations UK Ltd. v. Quigg*, 894 F.2d 392 (Fed. Cir. 1990) is controlling precedent that mandates the grant of a patent term extension for Photocure's U.S. Patent No. 6,034,267?

2) Did the district court correctly hold that, even if this were a case of first impression, the plain meaning of the relevant language in 35 U.S.C. § 156 requires that an "active ingredient" be a compound actually present in a drug product relied upon to support a patent term extension application, and not an "active moiety" produced by the body after the drug product is administered, and that Photocure is thus entitled to a patent term extension?

STATEMENT OF THE CASE

I. The Parties' Contentions

This case involves interpretation of the patent term extension provisions of the 1984 Drug Price Competition and Patent Term Restoration Act (also known as the "Hatch-Waxman Act") (Pub. L. No. 98-417, 98 Stat. 1585). These provisions are codified at 35 U.S.C. § 156. The stated purpose of these provisions was "to create a new incentive for increased expenditures for research and development of certain products which are subject to premarket government approval. The incentive is the restoration of some of the time lost on patent life while the product is awaiting pre-market approval." H.R. Rep. No. 98-857, Pt. 1, at 14-15 (1984), *as reprinted in* 1984 U.S.C.C.A.N. 2647, 2647-48.

Under the statute, the drug product relied upon to support a patent term extension ("PTE") must be the "first permitted commercial use or marketing of the product." 35 U.S.C. § 156(a)(5)(A). The statute defines "product" to mean "active ingredient . . . including any salt or ester of the active ingredient." 35 U.S.C. § 156(f)(2). Accordingly, for a drug product to support a PTE, neither the active ingredient of the drug product nor any salt or ester of that active ingredient can previously have been approved.

Photocure contends that the "active ingredient" – as used in the statute – must be a compound that is actually present in the drug product at issue and that is

intended to produce a therapeutic effect. The Patent and Trademark Office ("PTO") contends that the "active ingredient" need not be in the drug product at issue, but rather may be the therapeutically active compound (*i.e.*, the "active moiety") that the body produces when it breaks down the product after administration. Photocure also contends that *Glaxo Operations UK Ltd. v. Quigg*, 894 F.2d 392 (Fed. Cir. 1990) (*Glaxo II*) resolved this question of statutory construction in Photocure's favor and is controlling precedent. The PTO contends that *Glaxo II* did not address the question of statutory construction at issue here.

II. The Proceedings Below

In 2004, Photocure applied for a patent term extension for its U.S. Patent No. 6,034,267 ("the '267 patent") based on the 4½-year period it spent obtaining regulatory approval of its METVIXIA drug product. (A459-68.) METVIXIA is a cream that is used to treat skin diseases. (A795.) The cream is applied to the diseased skin, and then light is shone on that skin, which helps kill diseased cells. (A796-98, A803-04.) METVIXIA contains methyl aminolevulinate hydrochloride ("MAL HCl"). (A5.) The '267 patent claims compositions including MAL HCl, and methods of treating skin diseases using MAL HCl. (A3.)

Prior to the regulatory approval of METVIXIA, a product (LEVULAN) containing aminolevulinic acid hydrochloride ("ALA HCl") was approved. (A5.) MAL HCl is a salt and an ester of a compound named aminolevulinic acid

("ALA"), and ALA HCl is a salt of ALA. (A3-4.) However, neither METVIXIA nor LEVULAN contain ALA. (A3-4, A15.) The PTO suggests that, when METVIXIA and LEVULAN are administered to patients, MAL HCl and ALA HCl are broken down by the body into ALA, and that ALA then functions as the therapeutically active compound. (PTO Br. at 6-9, 17.)

A PTE application must satisfy a number of requirements to be approved. 35 U.S.C. § 156(a). As noted above, one of these requirements is that the drug product approval being relied upon to support the PTE must be "the first permitted commercial marketing or use of the product." 35 U.S.C. § 156(a)(5)(A). It is undisputed that Photocure's application satisfies the requirements for a patent term extension other than this "first permitted commercial marketing" requirement. (A1.) Thus, the sole issue in this case is whether Photocure's application satisfies this requirement. (A1.)

In making its decision as to whether a patent is eligible for an extension, the PTO seeks input from the Food and Drug Administration ("FDA") on certain requirements that are within the FDA's "expertise and records" pursuant to a Memorandum of Understanding between the PTO and the FDA. 52 Fed. Reg. 17,830 (1987). One of these is the "first permitted commercial marketing" requirement.

Accordingly, after receiving Photocure's PTE application, the PTO sought input from the FDA. (A515-16.) In response, the FDA informed the PTO that the active ingredient in METVIXIA is MAL HCl and that the active ingredient in LEVULAN is ALA HCl. (A517.) This is noteworthy because it is totally inconsistent with the position the PTO now takes before this Court, which is that the "active ingredient" in both METVIXIA and LEVULAN is ALA. (PTO Br. at 6-9, 17.) The FDA nevertheless concluded that METVIXIA did not satisfy the "first permitted commercial marketing" requirement because MAL HCl is an ester of ALA HCl, which had previously been approved. (A517.)

After receiving the FDA's input, the PTO initially denied Photocure's PTE application on the same basis that the FDA had suggested. (A518-20.) In particular, in a "Notice of Final Determination -- Ineligible", the PTO stated that METVIXIA did not satisfy the "first permitted commercial marketing" requirement because the active ingredient in METVIXIA – MAL HCl – was an ester of the active ingredient – ALA HCl – in LEVULAN, which had previously been approved:

> 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 is [sic] the same product as aminolevulinic acid hydrochloride. As noted in the FDA letter, the active ingredient LEVULAN® had been approved for commercial marketing and use prior to the approval of the applicant's product.

(A519.)

Once again, this is noteworthy because it is totally inconsistent with the position the PTO now takes before this Court, which is that the active ingredient in both METVIXIA and LEVULAN is ALA. (PTO Br. at 17.) The PTO has since repudiated this initial decision, and the basis of that decision is not at issue in this case.[1] (A898.)

Photocure then filed a "Request for Reconsideration." (A521-26.) In a "Final Decision," the PTO again denied the application for alleged failure to satisfy the "first permitted commercial marketing" requirement. (A741-49.) In this decision, the PTO relied for the first time on this Court's decision in *Pfizer Inc. v. Dr. Reddy's Labs., Ltd.*, 359 F.3d 1361 (Fed. Cir. 2004) ("*Pfizer II*"), a case involving the scope of the patent owner's rights during a patent term extension. (A745.) Both the FDA and the PTO had previously cited *Glaxo II* in support of their decisions, a case involving the "first permitted commercial marketing" requirement, not *Pfizer II*. (A517, A519.) The PTO held that the active ingredient

[1] To be clear, the basis of the initial decision was that the relevant inquiry is whether the active ingredient of the previously-approved drug product or a salt or ester of that active ingredient is in the drug product being relied upon to support the extension, and that Photocure's PTE application should thus be denied because MAL HCl was an ester of the previously-approved ALA HCl (*i.e.*, one starts from the previously-approved drug product and looks forward). However, the proper inquiry is whether the active ingredient of the drug product at issue or a salt or ester of that active ingredient have previously been approved (*i.e.*, one starts from the drug product at issue and looks backward).

in both METVIXIA and LEVULAN is ALA because ALA is the "active moiety" for both drug products.

Photocure challenged the PTO's decision in the U.S. District Court for the Eastern District of Virginia. (A2.) The court granted summary judgment in Photocure's favor, holding that this Court's decision in *Glaxo II* was controlling precedent. (A1.) The district court then held that, under *Glaxo II*, "active ingredient" as used in 35 U.S.C. § 156(f)(2) refers to a compound that itself is present in the drug product at issue, and not a compound that is produced when the drug product is administered to patients (*i.e.*, not the "active moiety"). (A14-15.) The court therefore found that the active ingredient in METVIXIA is MAL HCl, and that the active ingredient in LEVULAN is ALA HCl. (A15.) Because neither MAL HCl nor a salt or ester had been previously approved, the approval of METVIXIA therefore satisfied the "first permitted commercial marketing" requirement. (A15.)

In making this determination, the district court recognized that the *Pfizer II* decision may have adopted an "active moiety" construction of "active ingredient" at odds with this Court's construction of "active ingredient" in *Glaxo II*. (A14.) The district court applied *Glaxo II*, and not *Pfizer II*, in accordance with this Court's rule that a prior decision of a panel of the Court is binding precedent on subsequent panels unless the prior decision is overturned *en banc*. (A14-15.)

The district court also held that, even if this had been a matter of first impression, the court would have found in Photocure's favor because the plain meaning of the term "active ingredient" requires a compound that is actually present in the drug product at issue, while the PTO's "active moiety" approach did not require the "active ingredient" to be actually present in the drug product. (A16.) Moreover, the Court held that "active ingredient" should not be interpreted to mean "active moiety" when both terms had well-known meanings at the time the statute was adopted, and Congress chose to use "active ingredient," not "active moiety." (A16.)

The district court thus held that Photocure's application satisfied the "first permitted commercial marketing" requirement. Since it was not disputed that the '267 patent meets the other requirements for a PTE, the court held that Photocure's application should be granted and remanded to the PTO for a ruling consistent with the court's opinion. (A1.)

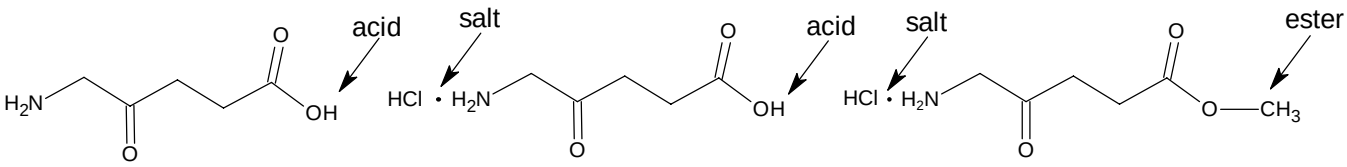
The PTO appealed the district court's ruling to this Court.

STATEMENT OF FACTS

I. The Chemical Compounds in METVIXIA and LEVULAN

Photocure's METVIXIA drug product contains MAL HCl. (A5.) METVIXIA received FDA approval in 2004. (A5.) The LEVULAN drug product, which is marketed by Dusa Pharmaceuticals, Inc., contains ALA HCl. (A5; A789.) LEVULAN was approved in 1999. (A789.)

MAL HCl is an ester and a salt of the acid ALA. (A5.) ALA HCl is a salt of ALA. (A3-4.) ALA HCl is not the same as, nor is it an ester or salt of MAL HCl. (A3-4, A9, A15.) The chemical structures of ALA, ALA HCl, and MAL HCl are diagrammed below. (A3-A4.)



aminolevulinic acid ("ALA")

ALA hydrochloride ("ALA HCl")

methyl aminolevulinate hydrochloride ("MAL HCl")

MAL HCl is actually present in METVIXIA and is intended to produce a therapeutic effect. (A5.) ALA is not present in METVIXIA. (A15.) As

diagrammed above, the structure for ALA has a –COOH group[2] (an acid group) on the right-hand side. (A3.) In MAL HCl, this –COOH group is replaced by a $–COOCH_3$ group. (A4.) In other words, the hydrogen atom (the "H") from the –COOH group in ALA is replaced by a methyl group (the "CH_3"). (A4.) Instead of a hydrogen atom being covalently bonded to the oxygen atom, a carbon atom is covalently bonded to the oxygen atom, and then three hydrogen atoms are covalently bonded to the carbon atom. (A4.) This change is known as esterification, and it is the change that makes MAL HCl an ester. (A4.) The other difference between ALA and MAL HCl is that ALA has an NH_2 group on one end with nothing bonded to it, while MAL HCl has that same NH_2 group with hydrochloric acid (HCl) ionically bonded to it.[3] (A3-4.) This change is known as salification, and it is the change that makes MAL HCl a salt (ALA HCl also has this change). (A4.) Thus, a compound with the chemical structure of ALA is not present in METVIXIA. (A15.)

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[2] The "C" in the –COOH group is a carbon atom located on the right-hand side of the ALA molecule at the joint between the double bond to one oxygen atom, and the single bond to another oxygen atom. By convention, carbon and hydrogen atoms are often not depicted by letter in such diagrams.

[3] To be precise, HCl donates the proton from its hydrogen atom to the NH_2 group, so that the NH_2 group becomes positively-charged NH_3+, which is ionically bonded to the remaining chloride ion (Cl-), which is negatively charged because it still contains the electron from the hydrogen atom. (A803.)

Before METVIXIA was approved, no product had been approved containing MAL HCl, or a salt or ester of MAL HCl. (A9, A15.)

II. The METVIXIA Drug Product

METVIXIA is used to treat skin diseases. (A795.) The product is a cream that is applied to the skin. (A795-97.) MAL HCl then passes through the skin and concentrates in cells to be treated. (A803-04.) Although the precise mechanism by which MAL HCl works is unknown, these cells use MAL HCl to build an excess amount of a naturally-occurring, light-sensitive compound (protoporphyrin IX). (A803-04.) Light is then shone on the skin, which activates the compound, resulting in a chemical chain reaction that ultimately kills the cells to be treated. (A798, A803-04.) The elimination of cells by activation of a light-sensitive compound is referred to as "photodynamic therapy." (A795.)

The approval of METVIXIA was the culmination of a research and development project that spanned over a decade. The first foreign application leading to the '267 patent was filed on March 10, 1995 (with the actual scientific research beginning earlier). (A469-502; A527-28.) The '267 patent issued on March 7, 2000. (A469.) Photocure applied for FDA approval of METVIXIA in 2000, and received such approval in 2004. (A504-14.) In its NDA for Metvixia, Photocure did not rely on the clinical trials and data that had been submitted in

support of the LEVULAN NDA, but rather conducted its own clinical trials and generated its own data.

MAL HCl provides many advantages over ALA HCl, and thus METVIXIA provides many advantages over LEVULAN. (A527-33.) These advantages include greater selectivity of uptake by cells to be treated and reduced systemic distribution, so that normal cells are less damaged by treatment than with LEVULAN (A529-32); greater penetration of cells to be treated, resulting in increased effectiveness of the treatment (A530-31); and reduced pain resulting from treatment. (A532.)

The FDA's Electronic Orange Book identifies MAL HCl as the active ingredient of METVIXIA (A791), and ALA HCl as the active ingredient of LEVULAN.[4] (A789; *see also* A793-832 at A810 [FDA-approved prescribing information for METVIXIA identifying the "active ingredient" as MAL HCl].)

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[4] *See also* http://www.accessdata.fda.gov/scripts/cder/ob/docs/querytn.cfm (last visited July 23, 2009). Before the district court, the PTO objected when Photocure cited to these Electronic Orange Book entries because Photocure had not submitted them to the PTO when the PTO was considering Photocure's PTE application, and thus had not made them part of the administrative record. (A893.) However, as Photocure explained before the district court, because the PTO's initial decision identified MAL HCl as the active ingredient in METVIXIA and ALA HCl as the active ingredient in LEVULAN (A519), Photocure had no reason to submit these entries in support of this apparently undisputed fact. (A950-52.) The entries only became relevant ***after*** the PTO issued its final decision, in which it for the first time asserted that ALA was the (continued…)

Moreover, during the proceedings before the PTO regarding Photocure's PTE application, both the FDA and the PTO stated that the active ingredient of METVIXIA was MAL HCl, and that the active ingredient of LEVULAN was ALA HCl. (A517, A519.) The PTO later reversed course, and asserted that the active ingredient in both is ALA. (A743.)

SUMMARY OF THE ARGUMENT

The district's court's judgment should be affirmed because, as the court correctly held (A14-15), *Glaxo II* is controlling precedent that mandates a judgment in Photocure's favor under the principle of stare decisis. The undisputed facts here are virtually identical to those in *Glaxo II*, and the legal issue is the same. In *Glaxo II*, Glaxo sought a patent term extension based on the regulatory review of a product containing an ester of the compound cefuroxime where a salt of cefuroxime had previously been approved. The PTO denied Glaxo's PTE application, holding that it did not satisfy the "first permitted commercial marketing" requirement. The district court reversed, and this Court affirmed.

In so doing, this Court construed the exact same portion of the patent term extension statute at issue here – namely, the definition of "product" as "the active ingredient. . . including any salt or ester of the active ingredient" – and held that

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"active ingredient" in METVIXIA. (A743.) Photocure did not have an
(continued…)

the "product" at issue had not been previously approved. In particular, this Court rejected the PTO's contention – which it raises again here – that regulatory review of a product cannot support a patent term extension if the product contains the same "active moiety" as a previously-approved product.

Here, Photocure is seeking a patent term extension based on regulatory review of an ester and salt of a compound where a salt of the compound had been previously approved. Under *Glaxo II*, the "first permitted commercial marketing" requirement is clearly satisfied in such circumstances, and thus Photocure is entitled to an extension and the district court should thus be affirmed.

Because *Glaxo II* is controlling precedent, this Court's later decision in *Pfizer II* is not controlling precedent, since a later panel decision cannot overrule an earlier panel decision. Moreover, even if *Glaxo II* were for some reason not controlling precedent, and this was instead a case of first impression, Photocure is entitled to an extension, as the district court correctly held. (A16.)

The statute provides that an extension may be based on regulatory review of a drug product if there has been no previous approval of the product's "active ingredient. . . including any salt or ester of the active ingredient." As the district court held, the term "active ingredient" has a plain meaning, and refers to a

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opportunity to supplement the administrative record at that point. (A518.)

compound that is actually present in the product and that is intended to provide a therapeutic effect. (A16.) The plain meaning of a statute should be followed except in rare and exceptional circumstances. Under this plain meaning, the active ingredient in METVIXIA is MAL HCl since MAL HCl is actually present in METVIXIA and since it is intended to provide a therapeutic effect. The active ingredient is not ALA, since ALA is not present in METVIXIA. Accordingly, Photocure is entitled to an extension, since neither MAL HCl, nor any salt or ester of MAL HCl, had previously been approved.

The PTO argues that the term "active ingredient" in the phrase "active ingredient. . . including any salt or ester of the active ingredient" should be interpreted to mean "active moiety," meaning the compound that produces a therapeutic effect when a drug product is administered, which can be a compound produced ***after*** the product is administered. As the district court correctly held, this argument is contrary to the plain meaning of the statute, since it would permit the "active ingredient" of a product to be a compound that is not actually present in the product. Thus, the PTO's "active moiety" approach should be rejected. Moreover, both "active ingredient" and "active moiety" had well-known meanings at the time the Hatch-Waxman Act was adopted, yet Congress chose to include "active ingredient" in the statute, not "active moiety." This strongly suggests that Congress did not intend for "active ingredient" to mean "active moiety."

The PTO puts forward a host of reasons for why its "active moiety" approach should be adopted, but all of these were considered and rejected in *Glaxo II*. Thus, even if this was a case of first impression, this Court should reject the PTO's arguments for the same reasons they were rejected in *Glaxo II*.

ARGUMENT

I. Standard of Review

The district court granted summary judgment to Photocure. (A1.) The parties agree that there are no genuine issues of material fact, and that this case turns on statutory interpretation. (A871-72.) This Court reviews a district court's grant of summary judgment based on statutory interpretation without deference to the district court. *See Glaxo II*, 894 F.2d at 395.

II. The District Court Correctly Held That *Glaxo II* Is Controlling Precedent That Mandates Judgment in Photocure's Favor

A. *Glaxo II* Is Controlling Precedent

The time spent obtaining FDA approval of a product may support a patent term extension if the approval is "the first permitted commercial marketing or use of the product." 35 U.S.C. § 156(a)(5)(A). The sole issue in this case is whether the approval of Photocure's METVIXIA "product" satisfies this "first permitted commercial marketing" requirement. The statute defines "product" as "drug product," and then defines "drug product" as "active ingredient. . . including any salt or ester of the active ingredient." 35 U.S.C. § 156(f)(2). Thus, to determine

whether the approval of the METVIXIA "product" may support a PTE, one must construe this statutory language – namely, "active ingredient. . . including any salt or ester of the active ingredient" – and apply it to the undisputed facts here.

In *Glaxo II*, this Court interpreted this exact same statutory language, applied it to facts that are virtually identical to those here, and held that a PTE was required by the statute. As the district court held in this case, the *Glaxo II* case is controlling, and must be followed.

1. The Facts of *Glaxo II* Were Nearly Identical to the Facts Here

In *Glaxo II*, Glaxo sought a PTE based on the time it took for its drug product (CEFTIN) containing cefuroxime axetil to be approved by the FDA. Cefuroxime axetil is an ester of cefuroxime, which the PTO contended was the active moiety of CEFTIN (just as MAL HCl is an ester of ALA,[5] which the PTO asserts is the active moiety of METVIXIA). Two drug products (ZINACEF and KEFUROX) containing salts of cefuroxime had previously been approved by the FDA (just as ALA HCl, a salt of ALA, has been previously approved).

The PTO denied the PTE application, holding that the FDA's approval of CEFTIN did not satisfy the "first permitted commercial marketing" requirement.

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[5] MAL HCl is also a salt of ALA. Thus, MAL HCl is both a salt and an ester of ALA, while cefuroxime axetil was just an ester of cefuroxime. This very (continued…)

The PTO first noted that the statute equates "product" with "active ingredient. . . including any salt or ester of the active ingredient," and then construed "active ingredient. . . including any salt or ester of the active ingredient" to mean all acid, salt and ester forms of the active moiety yielded when the drug product is administered. *See Glaxo Operations UK Ltd. v. Quigg*, 706 F. Supp.1224, 1226 (E.D. Va. 1989) ("*Glaxo I*"), *aff'd*, 894 F.2d 392 (Fed. Cir. 1990). Since salt forms of cefuroxime had been previously approved (*i.e.*, ZINACEF and KEFUROX), the PTO rejected the PTE application. *Id.* The district court reversed, holding that the PTO's position was inconsistent with the plain meaning of the statutory language. *Id.* at 1227-28.

2. The PTO's Position Before This Court in *Glaxo II* Was Substantively Identical to Its Position Here

On appeal before this Court, the PTO argued that Glaxo was not entitled to a PTE because it contained an ester of an active moiety that had previously been approved. This Court stated the PTO's position as follows:

> The Commissioner, on the other hand, argues that "product" was not intended by Congress to have a literal meaning, *only* encompassing three categories of compounds: (1) an active ingredient; (2) a salt of an active ingredient; or (3) an ester of an active ingredient. He asserts that Congress intended the definition to mean any "new chemical entity," i.e., "new active moiety," which would encompass *all* acid, salt, or ester forms of a single

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slight factual difference between *Glaxo II* and the present case is irrelevant, and the PTO has never contended to the contrary.

> therapeutically active substance even if the drug before being administered contained only other substances. In this case, because after being orally administered CEFTIN tablets combine with digestive substances in the human body to produce the same therapeutically active substance contained in both ZINACEF and KEFUROX, then under the Commissioner's interpretation, Glaxo has already had a prior approval of the "product" before it sought a term extension for its '320 patent.

894 F.2d at 394.

This position is substantively identical to the position the PTO is taking in this appeal. In both cases, the PTO's position is that the phrase "active ingredient… including any salt or ester of the active ingredient" encompasses all acid, salt and ester forms of the same active moiety. In *Glaxo II*, the PTO's position was that all acid, salt and ester forms of cefuroxime were encompassed by the phrase, and that CEFTIN could not support a PTE because a salt form of cefuroxime had previously been approved. Here, the PTO's position is that all acid, salt and ester forms of ALA are encompassed by the phrase, and that METVIXIA cannot support a PTE because a salt form of ALA had previously been approved.

3. This Court Rejected the PTO's Position in *Glaxo II*, and Held That Under the Plain Meaning of the Statute, Each Salt or Ester Is A Different "Active Ingredient"

In *Glaxo II*, this Court squarely rejected the PTO's position. In so doing, the Court construed the phrase "active ingredient. . . including any salt or ester of the active ingredient." The Court stated that "the terms 'active ingredient,' 'salt,'

and 'ester' had well-defined, ordinary, common meanings when Congress enacted the Act," and then included the following citation: "45 Fed. Reg. 72,582; 72,591 (1980); 44 Fed. Reg. 2932, 2937-38 (1979); *Chemical Dictionary, supra* note 3, at 418, 907." *Id.* at 395; *see also id.* at 397 (citing same three sources for the proposition that "the terms Congress used. . . were all well-known and well-defined at the time the Act was passed."). The "Chemical Dictionary" citation provided definitions for "salt" and "ester," and thus it is clear that the "well-defined, ordinary, common" meaning of "active ingredient" was articulated in the two cited Federal Register excerpts.

The first of these two excerpts states that different salts or esters of the same "therapeutic moiety" are different "active drug ingredients":

> ***[T]he same therapeutic moiety may appear in slightly different chemical forms, e.g., as different salts or esters of the same molecule. To distinguish these separate forms, the term 'active drug ingredient' is used; each salt or ester of a therapeutic agent is a unique active drug ingredient.*** For example, tetracycline hydrochloride and tetracycline phosphate complex are distinct active drug ingredients containing the same therapeutic moiety.

(A996-98 [44 Fed. Reg. 2932, 2937-38 (1979)] (emphasis added).)

Similarly, the second excerpt states that, to be "identical drug active ingredients," two ingredients must be the same salt or ester of the same "therapeutic moiety":

> Cyanocobalamin and cobalamin concentrate. . . are not drug products that contain identical amounts of the identical active ingredient, i.e., the same salt or ester of the same therapeutic moiety in identical dosage forms.

(A1000-01 [45 Fed. Reg. 72,582, 72,591 (1980)].)

These excerpts show that, in *Glaxo II*, this Court held that, under the "well-defined, ordinary, common" meaning of "active ingredient," each different salt or ester of a single therapeutic moiety is a different active ingredient. The Court also rejected the PTO's assertion that the phrase "active ingredient. . . including any salt or ester of the active ingredient" should be given an interpretation different from the "combined, common and ordinary meanings" of the terms in the phrase. *Id.* at 395. Accordingly, the Court held that the plain meaning of the statutory language dictated a judgment in Glaxo's favor. Although not explicitly stated in the opinion, this plain meaning was clearly that the ester cefuroxime axetil was the active ingredient in CEFTIN because "each salt or ester of a therapeutic agent is a unique active drug ingredient." And because neither cefuroxime axetil nor a salt or ester of cefuroxime axetil had been previously approved, Glaxo's PTE application satisfied the "first permitted commercial marketing" requirement.

In *Glaxo II*, this Court specifically rejected the PTO's position that the phrase "active ingredient. . . including any salt or ester of the active ingredient" encompassed all acid, salt and ester forms of the active moiety, stating as follows:

> The Commissioner, however, suggests that Congress "inartfully" and "awkwardly" selected this combination of terms intending something other than their combined, common and ordinary meanings. . . This approach is unpersuasive because it simply overlooks the legal consequence that ordinarily attaches whenever statutory language has a clear and plain

> meaning. Instead, the Commissioner simply ignores the plain meaning of these terms and argues, as a totally unrelated question, that Congress intended a meaning contrary to the plain meaning.

Id. at 395.

The Court pointed out that if Congress had wanted to make only new "active moieties" or "new chemical entities" eligible to support a PTE, it could have used those terms (which were also well-known at the time) in the statute. Its choice of the phrase "active ingredient. . . including any salt or ester of the active ingredient" thus indicated that Congress did not intend to limit PTEs to new active moieties or new chemical entities:

> [W]e are hesitant to stray from the plain meaning of the statute because both the terms Congress used and the terms the Commissioner would have us substitute were all well-known and well-defined at the time the Act was passed. Nevertheless, 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.

Id. at 397.[6]

[6] *See also id.* at 398 ("In fact, if that were Congress' intent, one would expect it to use the same term – 'new chemical entity' – in the bill as is used in the House Report. Instead, the bill employed other terms with an equally clear but quite different meaning.") and 399 ("Congress specifically selected terms with narrow meanings that it chose from among many alternatives. Congress could have, but did not, select broad terms with a range of possible meanings.")

4. The PTO's Argument For Why *Glaxo II* Is Not Controlling Precedent Is Untenable

In the face of this overwhelming evidence that in *Glaxo II* this Court addressed the meaning of "active ingredient" (as well as the phrase "active ingredient. . . including any salt or ester of the active ingredient"), the PTO argues that *Glaxo II* did not address this issue because the parties agreed that the "active ingredient" in CEFTIN was cefuroxime axetil, and thus was undisputed. This is untenable.

The Court interpreted "active ingredient" (as well as the phrase "active ingredient. . . including any salt or ester of the active ingredient") for at least two different reasons. First, the Court interpreted "active ingredient" in rejecting the PTO's argument that the phrase "active ingredient. . . including any salt or ester of the active ingredient" means all acid, salt or ester forms of the active moiety of the drug product at issue, and in holding that each salt or ester is instead a separate active ingredient. Second, the Court held that "active ingredient" had a plain meaning in holding that the PTO's proffered construction was not entitled to deference under *Chevron U.S.A. Inc. v. Natural Res. Def. Council, Inc.*, 467 U.S. 837, 842-43 (1984).[7] *See Glaxo II*, 894 F.2d at 398. Thus, not only did the Court

[7] The district court's decision in *Glaxo I* clearly did address the meaning of "active ingredient" because, at the district court level, the parties sharply disagreed on the identity of the active ingredient in the drug product at issue. 706 F. Supp. at 1227. This Court endorsed the district's court's statutory (continued…)

interpret "active ingredient" (and "active ingredient. . . including any salt or ester of the active ingredient") in *Glaxo II*, but that interpretation was essential to the Court's judgment, and not mere dicta.

Although the parties may have agreed on the identity of the "active ingredient" in CEFTIN, they most certainly did not agree on how the relevant statutory language – including "active ingredient" – should be interpreted. As explained above, the sole issue in the case was whether "active ingredient. . . including any salt or ester of the active ingredient" should be construed to encompass all acid, salt and ester forms of the active moiety (as the PTO contended), or whether it should be construed to encompass only the particular form included in the drug product at issue, and any salts or esters of that form (as Glaxo contended).

Indeed, this Court specifically noted that its task was to decide the question of statutory interpretation that had been decided by the district court. *Id.* at 395 ("this court need only decide the same question of law decided by the district court on summary judgment. That question is one of statutory interpretation . ."). And

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construction and analysis. *See Glaxo II*, 894 F.2d at 393 ("Because the district court correctly construed and properly applied the operative terms of the Act, we affirm."). In this way as well, this Court in *Glaxo II* addressed the meaning of "active ingredient." Finally, this Court also relied on the plain meaning of
(continued…)

the question of statutory interpretation decided by the district court was clearly the meaning of "active ingredient" and "active ingredient. . . including any salt or ester of the active ingredient." *See Glaxo I*, 706 F. Supp. at 1227-28. If the question of statutory interpretation decided by the Court in *Glaxo II* did not involve the proper construction of "active ingredient" or "active ingredient. . . including any salt or ester of the active ingredient," as the PTO now contends, then it is difficult to see what the question could possibly have been.[8]

The PTO's current position that *Glaxo II* did not address the meaning of "active ingredient" (PTO Br. 21-24) is also belied by the position the PTO took in denying a 2005 PTE application, wherein the PTO stated that "*Glaxo* must be treated as overruled" by *Pfizer II*.[9] (A853-55 at A855.) If the PTO thought *Glaxo II* was overruled by *Pfizer II* – which the PTO contends addressed the meaning of "active ingredient" – then surely it must have believed that *Glaxo II* addressed the meaning of "active ingredient" as well.

"active ingredient" in setting the proper approach to reviewing the legislative history. *Id.* at 396.

[8] The PTO asserts that, in *Glaxo II*, "the parties' arguments focused solely on whether the term 'product' in Section 156(a)(5). . . meant the precise product approved by FDA." (PTO Br. at 22.) However, the PTO does not cite to anything in *Glaxo II* to support that assertion, and Photocure has been unable to find any discussion of that "issue" in *Glaxo II*.

B. Under *Glaxo II*, Photocure Is Entitled to a Patent Term Extension

The parties agree that the sole issue here is one of statutory construction. As the district court held, when the construction of the statute enunciated in *Glaxo II* is applied to the undisputed facts here, it is clear that Photocure is entitled to a patent term extension. (A15.) Under *Glaxo II*, the "active ingredient" in METVIXIA is MAL HCl, since each acid, salt or ester form of an active moiety is treated as a different active ingredient, and since the form present in METVIXIA is MAL HCl. It is undisputed that neither MAL HCl, nor any salt or ester of MAL HCl, have been previously approved (just as neither cefuroxime axetil, nor any salt or ester of cefuroxime axetil had been previously approved in *Glaxo II*). Accordingly, Photocure's PTE application satisfies the "first permitted commercial marketing" requirement, and should be granted.

III. The District Court Correctly Held That, Even if This Was a Case of First Impression, the Plain Meaning of the Statute Mandates Judgment in Photocure's Favor

A. If *Glaxo II* Is Not Controlling Precedent, Then Neither Is *Pfizer II*

The PTO argues that *Pfizer II* is controlling precedent here. However, as explained above, *Glaxo II* is controlling precedent here. Because both *Glaxo II* and *Pfizer II* were panel decisions, and because *Glaxo II* came before *Pfizer II*,

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[9] The PTO abandoned this position after the PTE applicant informed it that a later panel decision cannot overrule an earlier one. (A906-14 at A911.)

Glaxo II must be considered controlling precedent, as the district court held. (A14-15.) *See Newell Cos., Inc. v. Kenney Mfg. Co.*, 864 F.2d 757, 765 (Fed. Cir. 1988); Fed. Cir. R. 35(a)(1).

However, if for some reason *Glaxo II* is held to not be controlling precedent due to some minor difference between *Glaxo II* and the present case (*e.g.*, the parties' agreement in *Glaxo II* that the active ingredient in CEFTIN was cefuroxime axetil), then *Pfizer II* should also be held to not be controlling precedent because that case is much more different from the present case than *Glaxo II*. Indeed, any statements in *Pfizer II* about the meaning of "active ingredient" are arguably dicta.

Unlike the present case, *Pfizer II* did not deal with the "first permitted commercial marketing" requirement of 35 U.S.C. § 156(a)(5)(A). Rather, *Pfizer II* dealt with the scope of rights to which a patent owner was entitled during the extended term of a patent that had been extended pursuant to 35 U.S.C. § 156(b). That sub-section 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. Pfizer had obtained a PTE 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.

Section 156(a)(5)(A) clearly contains a "product" limitation, in that it limits eligibility for a patent term extension to the "first permitted commercial marketing" of the product at issue. Thus, this Court in *Glaxo II* was required to construe "product," and thus "active ingredient. . . including any salt or ester of the active ingredient." However, it is not so clear that section 156(b) contains a "product" limitation. The relevant language 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—(1) in the case of a patent which claims a product, be limited to any use approved for the product. . .". 35 U.S.C. § 156(b). In the *Pfizer II* case, one of the critical issues was whether this language limited the scope of an extended patent only to the approved use and thereby excluded unapproved uses (*i.e.*, whether it included only a "use" limitation), or whether this language limited the scope of an extended patent to the approved use and to the approved product (*i.e.*, whether it included a "use" and a "product"

limitation).[10] The district court held that this language contained both a "use" limitation and a "product" limitation. *See Pfizer v. Dr. Reddy's Labs., Ltd.* ("*Pfizer I*"), 2002 Extra LEXIS 610, *11-16 (D.N.J. Dec. 17, 2002), *rev'd*, 359 F.3d 1361 (Fed. Cir. 2004). This Court reversed, holding that it contained only a "use" limitation. *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). This holding, which was sufficient to resolve the dispute between the parties, is not inconsistent with the holding in *Glaxo II.* Because the holding in *Pfizer II* regarding the scope of the "rights derived" provision was sufficient to resolve the dispute between the

[10] An example may help clarify this distinction. Suppose a patent has a claim to using either active ingredient A or B for use X or Y. During the original term of the patent, the claim would cover using active ingredient A for uses X and Y, and using active ingredient B for uses X and Y. Suppose the patent is then extended based on the approval of a drug product that contains active ingredient A approved for use X. If section 156(b) contains only a "use" limitation, then during the extended term, the patent will cover using active ingredient A in use X, and using active ingredient B in use X (*i.e.*, the "use" limitation will only eliminate the portion of the claim that covered un-approved use Y). However, if section 156(b) contains both a "use" limitation and a "product" limitation, then during the extended term, the patent will cover only using active ingredient A in use X (*i.e.*, the "use" limitation will eliminate the portion of the claim that covered un-approved use Y, and the "product" limitation will eliminate the portion of the claim that covered the use of un-approved active ingredient B).

parties, the language in *Pfizer II* about the meaning of "active ingredient" can be viewed as mere dicta.[11]

The PTO attempts to find support for its argument that *Glaxo II* did not address the meaning of "active ingredient" (see above) in the fact that *Glaxo II* was not even mentioned in the *Pfizer II* opinion even though *Glaxo II* was extensively referred to in the district court opinion and the parties' briefs, arguing that this shows that *Glaxo II* did not address the meaning of "active ingredient." (PTO Br. at 23-24.) However, a more logical explanation for this fact is that the holdings in the two cases were not inconsistent because the Court's interpretation of the "rights derived" provision in *Pfizer II* (which was not at issue in *Glaxo II*) was sufficient to resolve the case in *Pfizer II*.

B. The District Court Correctly Held That the Plain Meaning of the Statute Mandates Judgment in Photocure's Favor

The district court held that even if this was a case of first impression, Photocure would be entitled to a patent term extension under the plain language of

[11] The Court in *Pfizer II* seemed to have been heavily influenced by the fact that Dr. Reddy's had relied on the safety and efficacy data for Pfizer's drug product (which contained amlodipine besylate) to support its request for approval of its drug product (which contained amlodipine maleate). The Court perceived an unfairness in permitting Dr. Reddy's to rely on Pfizer's clinical data, but at the same time holding that Pfizer's patent would only cover amlodipine besylate during its extended term. *See Pfizer II*, 359 F.3d at 1366. This is not an issue here, as Photocure did not rely on the safety and efficacy data for LEVULAN in its NDA, but rather generated and submitted its own data.

the statute. (A16.) The district court went on to hold that nothing in the legislative history shows that Congress intended the words of the statute to have other than their plain meaning, and that Photocure should thus prevail. (A16.) The district court's judgment should be affirmed on this basis as well.

1. The Plain Meaning of a Statute Should Be Followed Except in Rare and Exceptional Circumstances

In *Glaxo II*, this Court explained that the plain meaning of a statute must be followed "except in rare and exceptional circumstances":

> "When . . . the terms of a statute [are] unambiguous, judicial inquiry is complete, except in rare and exceptional circumstances." *United States v. James, 478 U.S. 597, 606, 92 L. Ed. 2d 483, 106 S. Ct. 3116 (1986)* (quoting *Rubin v. United States, 449 U.S. 424, 430, 66 L. Ed. 2d 633, 101 S. Ct. 698 (1981)* (internal quotation marks omitted)). Moreover, absent a "clearly expressed legislative intention to the contrary," a statute's plain meaning "must ordinarily be regarded as conclusive." *Consumer Prod. Safety Comm'n v. GTE Sylvania, Inc., 447 U.S. 102, 108, 64 L. Ed. 2d 766, 100 S. Ct. 2051 (1980).*

Glaxo II, 894 F.2d at 395.

As set forth below, this is not one of those rare and exceptional circumstances.

2. The Term "Active Ingredient" Had a Plain Meaning at the Time the Hatch-Waxman Act Was Adopted, and That Plain Meaning Mandates Judgment in Photocure's Favor

At the time the Hatch-Waxman Act was passed, the term "active ingredient" had a plain meaning, as this Court held in *Glaxo II*. This plain meaning was a compound actually present in a drug product that provides a therapeutic effect.

Under this plain meaning, an "active ingredient" is not something used to make a drug product that is not present in the drug product (like an intermediate), nor is it something that is produced by the body after the drug product is administered to a patient. Of most relevance to the present case, under this plain meaning, an "active ingredient" is the particular acid, salt or ester present in the drug product, and not all acids, salts or ester of the active moiety.

This plain meaning is demonstrated by a number of sources, including: (1) an FDA regulation in existence at the time the Act was passed setting forth the "established definition" of "active ingredient,"[12] which states that an "active ingredient" is a "component"[13] of a drug product; (2) the Federal Register notices relied on by the Court in *Glaxo II* for the plain meaning of "active ingredient,"[14] which state that "each salt or ester of a therapeutic agent is a unique active drug ingredient," and (3) a dictionary definition of the word "ingredient" relied on by

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[12] *See* 21 C.F.R. § 210.3(b)(7) ("Active ingredient means any component that is intended to furnish pharmacological activity. . ."). Notably, the FDA used this same definition – which it referred to as "the established definition of active ingredient" – when it adopted a regulation setting forth a definition of "active ingredient" as that term is used in the patent term extension statute. *See* 21 C.F.R. § 60.3(b)(2); 51 Fed. Reg. 25,338 (1986).

[13] *See The American Dictionary of the English Language* (3d ed. 1992) (defining "component" as "[a] constituent element.")

[14] *See* 45 Fed. Reg. 72,582; 72,591 (1980); 44 Fed. Reg. 2932, 2937-38 (1979).

the court in *Glaxo I*, which indicates that an ingredient is a "constituent element of a mixture."[15]

In *Glaxo I*, relying on the plain meaning of "ingredient," the district court rejected the PTO's argument that an "active ingredient" could be something that is produced after a drug product is administered to a patient, rather than a component of the drug product itself:

> 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.***

Glaxo I, 706 F. Supp. at 1227-28 (footnote omitted, emphasis added); *see also Glaxo II*, 894 F.2d at 393 ("Because the district court correctly construed and properly applied the operative terms of the Act, we affirm.").

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[15] *See Glaxo I*, 706 F. Supp. at 1227 (citing *Webster's Second University Dictionary* (1984)).

When the plain meaning of "active ingredient" is applied to the present case, it is clear that the active ingredient in METVIXIA is MAL HCl, since each salt or ester is a unique active ingredient, and since MAL HCl (and not ALA) is actually present in METVIXIA.[16] Because neither MAL HCl nor a salt or ester of MAL HCl has previously been approved, METVIXIA satisfies the "first permitted commercial marketing" requirement, and Photocure is entitled to a patent term extension.

3. The PTO's Miscellaneous Arguments for Why "Active Ingredient" Did Not Have the Plain Meaning Ascribed to It By the District Court Here and This Court in *Glaxo II* Should Be Rejected

The PTO makes several arguments for why "active ingredient" did not have the plain meaning set forth above. As explained below, each of these arguments should be rejected.

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[16] At one point, the PTO appears to concede that ALA is not in METVIXIA. (PTO Br. at 14 ["ALA in its non-salified, non-esterified form is not itself physically present in Metvixia."].) However, at other times, the PTO appears to be asserting that ALA is present in METVIXIA. (PTO Br. at 35 ["In any event, it is accurate to say that [the] active moiety is contained in the final compound in that it is present in the form of the particular salt or ester of the moiety."]). As explained above, there is no compound in METVIXIA having the chemical structure of ALA, and thus it is not correct to say that ALA is present in METVIXIA. Indeed, in *Glaxo I*, the PTO admitted that cefuroxime (the active moiety) was not actually present in cefuroxime axetil (the ester). *See Glaxo I*, 706 F. Supp. at 1228. Moreover, the PTO's assertion is inconsistent with the FDA-approved prescribing information for METVIXIA, which does not list ALA as an ingredient of the product. (A810.)

First, the PTO argues that "[v]iewed in isolation, 'active ingredient' is an ambiguous term that could bear more than one meaning." (PTO Br. at 25.) However, the PTO does not cite to a single source that provides a definition of "active ingredient" that is inconsistent in any way with the plain meaning stated above.

Second, the PTO makes much of the fact that a portion of the dictionary definition of "ingredient" cited by the district court indicates that an ingredient is "[s]omething that ***enters into*** the formation of a compound or mixture" (PTO Br. at 34-35):

> The primary definition of the term "ingredient" requires that the ingredient actually be contained in the compound. *See* 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.")

(A16.)

The PTO argues that this definition shows that an "ingredient" need not actually be present in a drug product, but rather can just be something used in making a drug product. This is wrong for several reasons.

For one thing, the PTO's argument would mean that intermediates used in making a drug product were "ingredients" of that product, which is totally inconsistent with the usage of the term "ingredient" in the pharmaceutical field, where "ingredient" is used to refer to compounds that are actually present in the

product. *Glaxo I*, 706 F. Supp. at 1227-28 ("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.'") At most, the PTO's argument would mean that elements that are actually mixed together to make a product are ingredients, like hops and yeast in the PTO's beer analogy. It would not mean that a compound like ALA, which the PTO suggests is produced by the body after METVIXIA is administered, is an ingredient. Moreover, the PTO's argument is directly contrary to this Court's holding in *Hoechst-Roussel Pharms. Inc. v. Lehman*, 109 F.3d 756, 759 n.3 (Fed. Cir. 1997) that "[f]or purposes of patent term extension, this active ingredient must be present in the drug product when administered." Clearly, the portion of the dictionary definition cited by the district court that is most relevant to the present case is "a component part, constituent or element," and not the part seized upon by the PTO.

Third, the PTO argues that "active ingredient" should be interpreted to mean "active moiety" because that would ensure that all compounds with the same "activity" are treated as the same active ingredient. (PTO Br. at 26.) But it is wrong to say that all salts or esters of the same active moiety have the same "activity." Indeed, MAL HCl has a number of advantages over ALA HCl, some of which arguably make it have a different "activity" than ALA HCl. (A529-32.) Moreover, the PTO's argument proves too much because it would mean that

"active ingredient" in all portions of the statute should be interpreted to mean "active moiety," but even the PTO agrees that "active ingredient" does not have that meaning in most portions of the statute. (PTO Br. at 30-31.)

However, the PTO's primary argument for why the plain meaning of the term "active ingredient" should not control here is that the context in which the term is found – *i.e.*, followed by the clause "including any salt or ester of the active ingredient" – shows that "active ingredient" should be given a special meaning. As set forth in the following section, this argument should be rejected.

4. The PTO's Argument That the "Including" Clause Shows That "Active Ingredient" Should Not Be Given Its Plain Meaning Should Be Rejected

The PTO argues that "active ingredient" should be given a special meaning (*i.e.*, "active moiety") by virtue of the accompanying clause "including any salt or ester of the active ingredient." In particular, the PTO argues that the use of the phrase "active ingredient. . . including any salt or ester of the active ingredient" "strongly suggests" that the "active ingredient" must not be a salt or an ester. (PTO Br. at 25.) This seems to be based on the theory that the statutory language implies there is a salt and an ester of each active ingredient, and that the "active

ingredient" cannot be a salt or an ester because one cannot have a salt or an ester of a compound that is itself a salt or an ester.[17] This is wrong for at least two reasons.

First, many therapeutically active compounds that are not salts or esters cannot be salified or esterified because they lack the necessary chemical group. Indeed, the statute itself implies that there may be no salts or esters of any given "active ingredient" by referring to "any" salt or ester of the active ingredient, instead of "all" salts and esters of the active ingredient. Thus, the PTO's premise that all "active ingredients" must have a salt or an ester is erroneous. Second, salts of esters, and esters of salts are common. Indeed, MAL HCl is an ester of the salt ALA HCl. Thus, contrary to the PTO's suggestion, the "including" phrase has meaning when the "active ingredient" is a salt or ester. When the active ingredient is a salt, the "product" is the salt and any esters of the salt. And when the "active ingredient" is an ester, the "product" is the ester and any salts of the ester. And when the "active ingredient" is an acid, the "product" is the acid and any salts or esters of the acid.

In *Glaxo II*, this Court recognized this and rejected the PTO's argument that the "including" clause indicates that "active ingredient" should be given something

[17] The PTO implies on several occasions that the *Pfizer II* Court adopted this argument. (PTO Br. 15, 19-20). However, Photocure has not been able to find a single statement in *Pfizer II* to the effect that the "including" clause indicates that the "active ingredient" cannot be a salt or an ester.

other than its plain meaning. *Glaxo II*, 894 F.2d at 395 ("The Commissioner, however, suggests that Congress 'inartfully' and 'awkwardly' selected this combination of terms intending something other than their combined, common and ordinary meanings. . . This approach is unpersuasive. . .") and 398 ("Here, as we have already stated, section 156(f)(2)'s operative terms, individually and as combined in the full definition, have a common and unambiguous meaning. . .").

If anything, the "including" clause shows that Congress did not intend that "active ingredient" mean "active moiety," as the PTO now argues. If Congress intended "active ingredient" to mean "active moiety," then the "including" clause would be superfluous because the term "active moiety" by itself[18] would pick up any salts or esters of the active moiety, and thus there would be no reason to add a clause referring to salts and esters of the active moiety. By contrast, Photocure's statutory interpretation gives meaning to the "including" clause in that it serves to "add" (i) salts to the definition of "product" when the "active ingredient" is an ester, (ii) esters to the definition of "product" when the "active ingredient" is a

[18] The FDA defines "active moiety" to mean "the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance." 21 C.F.R. § 314.108(a).

salt, and (iii) salts and esters to the definition of "product" when the "active ingredient" is an acid.

5. The Fact That "Active Moiety" Had a Plain Meaning at the Time the Hatch-Waxman Act Was Passed, Yet Congress Chose Not to Use That Term, Is Telling

The district court also found support for its holding in the fact that the statute did not use the well-known term "active moiety," but rather used the phrase "active ingredient. . . including any salt or ester of the active ingredient." The district court reasoned that, if Congress had intended for "product" to mean "active moiety" (as the PTO now contends it should be understood to mean), it would simply have used the term "active moiety" in the statute:

> Also worth emphasizing is that the term "active moiety" was indisputably well-known at the time Congress drafted the statute. If Congress desired to infuse the "active moiety" concept into §§ 156(a) and (f), it could have done so easily by including the term somewhere in either of those two provisions.

(A16[19].)

This logic – which, as discussed above, was also relied upon by this Court in *Glaxo II* – makes perfect sense, and provides further support for rejecting the PTO's "active moiety" approach. The PTO's only answer is to weakly assert that

[19] *See also Glaxo I*, 706 F. Supp. at 1228 ("[N]either this Court, nor the Commissioner is at liberty to ignore the plain meaning and the fact that the statute uses 'ingredient,' not 'moiety.' 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.")

Congress's use of "active ingredient" rather than "active moiety" "does not prove that Congress did not have 'active moiety' in mind or that 'active moiety' would *not* be a permissible understanding of what Congress meant. . .". (PTO Br. at 31.)

C. The PTO's Miscellaneous Arguments for Why It Should Prevail Should Be Rejected

1. The PTO's Reliance on the FDA's Interpretation of the "Marketing Exclusivity" Provisions of the Hatch-Waxman Act Should Be Rejected

The PTO asserts that the FDA has interpreted language in the "marketing exclusivity" provisions of the Hatch-Waxman Act that is similar to the key language here – "active ingredient. . . including any salt or ester of the active ingredient" – to mean "active moiety."[20] (PTO Br. at 26-29; 21 U.S.C. § 355(j)(5)(F)(i) and (ii); 21 C.F.R. § 314.108(a).) The PTO argues that the FDA's interpretation should be followed here because similar language in the same statute should be interpreted in the same manner. This argument should be rejected for a number of reasons.

[20] As the PTO acknowledges (PTO Br. at 7 n. 1), the FDA interprets the language in the "marketing exclusivity" provisions to be broader than the PTO is interpreting the key language in the patent term extension statute. For example, the FDA interprets the language in the "marketing exclusivity" provisions to generally preclude 5-year marketing exclusivity for an enantiomer where the racemate has been previously approved, while the PTO interprets the language in the patent term extension statute to permit a PTE for an enantiomer where the racemate has previously been approved.

First and foremost, the plain meaning of the statute should be followed except in rare and exceptional circumstances. *See Glaxo II*, 894 F.2d at 395. Interpreting "active ingredient" to mean "active moiety" – even if the FDA has done that – disregards the plain meaning of the term Congress chose to use.

Second, contrary to the PTO's argument, it is not a hard-and-fast rule that similar language in the same statute must be interpreted in the same way. *See Atlantic Cleaners & Dryers, Inc. v. United States*, 286 U.S. 427, 433-34 (1932); *Nike Inc. v. Wal-Mart Stores, Inc.*, 138 F.3d 1437, 1445-46 (Fed. Cir. 1998); *Libbey Glass v. United States*, 921 F.2d 1263, 1265 (Fed. Cir. 1990). Indeed, the PTO itself is arguing that "active ingredient" should be interpreted in one way in certain portions of the statute (*i.e.*, where it is not followed by the "including" clause), and a different way in other portions of the statute (*i.e.*, where it is followed by the "including" clause). (PTO Br. at 30-31.)

Third, there is no reason to think that the FDA's interpretation of that language is more likely to be correct than this Court's interpretation of that language in *Glaxo II*. In fact, there is every reason to think that the FDA – an administrative agency and a part of the executive branch – is more likely to be influenced by policy considerations than a court. In *Glaxo II*, this Court made this very point in rejecting the PTO's argument that the FDA's interpretation of the "marketing exclusivity" provision should be deferred to:

> The Commissioner attempts to bootstrap his claim of deference by emphasizing that the FDA has interpreted the nearly identical language of title I in a similar manner. He stresses that the FDA similarly has technical expertise. We are unpersuaded. 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 Commissioner's.

Glaxo II, 894 F.2d at 399, n. 11; *see also Abbott Labs. v. Young*, 691 F. Supp. 462, 470 (D.D.C. 1988), *remanded*, 920 F.2d 984 (D.C. Cir. 1990) (criticizing the FDA's interpretation of the "marketing exclusivity" provisions because "[a]lthough the FDA may state a logical policy for the application of the subsections at issue, that policy is entirely an invention of the Agency.").

Fourth, the FDA itself has for many years interpreted the phrase "active ingredient. . . . including any salt or ester of the active ingredient" in the patent term extension statute to have a different meaning than the similar phrase in the "marketing exclusivity" provisions, and in a manner favorable to Photocure. If one was going to look to the FDA for guidance in interpreting the patent term extension statute, it would make sense to examine how the FDA has interpreted that statute, and not how it has interpreted the "marketing exclusivity" provisions.

The FDA's interpretation of the phrase "active ingredient. . . including any salt or ester of the active ingredient," as used in the patent term extension statute, can be found in a number of places. For example, the FDA promulgated a regulation (21 C.F.R. § 60.3(b)(2)) in connection with its role in the patent term

extension process, 53 Fed. Reg. 7298 (1988), which defines "active ingredient" as "any component that is intended to furnish pharmacological activity. . .", and not as "active moiety."[21] The reference to "component" in the definition shows that the FDA does not define "active ingredient" in the patent term extension statute to be a compound that is only formed after administration of the drug product (*i.e.*, not "active moiety").[22] The PTO tries to downplay the significance of this regulation by pointing to the fact that the regulation was adopted before the FDA adopted its current regulations concerning the "marketing exclusivity" provisions. (PTO Br. at 29 n. 9.) This misses the mark because the FDA could have amended the definition of "active ingredient" in its patent term extension regulations at any time after it adopted its current "marketing exclusivity" regulations, but chose not

[21] Although the PTO has regulations implementing the patent term extension statute, 52 Fed. Reg. 9394 (1987); 37 C.F.R. §§ 1.710-1.791, it does not have a regulation defining "active ingredient." This is very likely because it relies upon the FDA to determine the identity of the "active ingredient" in the product pursuant to the Memorandum of Understanding between the two agencies. 52 Fed. Reg. 17,830 (1987). Here, of course, the FDA stated that MAL HCl is the active ingredient in METVIXIA, and that ALA HCl is the active ingredient in LEVULAN. (A517.)

[22] The definition goes on to state that "[t]he 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)). This clearly is not referring to compounds that are only produced after the drug product is administered to patients.

to do so, even though it amended its patent term extension regulations during that period. 64 Fed. Reg. 396, 399 (1999).

Similarly, the FDA's web site contains the following paragraph about the patent term extension statute:

> A product is the active ingredients contained therein ***for patent term extension purposes. Active ingredient does not equal active moiety*** (generally the molecule or ion responsible for the physiological or pharmacological action). A new ester or salt of a previously approved acid is eligible for patent extension; a new acid of a previously approved salt or ester is ineligible.

Small Business Assistance: Frequently Asked Questions on the Patent Term Restoration Program, Question 7 (emphasis added), http://www.fda.gov/drugs/developmentapprovalprocess/smallbusinessassistance/ucm069959.htm (last visited July 25, 2009).

Finally, in this case, when the FDA was asked by the PTO to weigh in on whether METVIXIA satisfied the "first permitted commercial marketing" requirement, it responded that the "active ingredient" in METVIXIA was the ester MAL HCl, and that the "active ingredient" in LEVULAN was the salt ALA HCl. (A517.) Notably, it did not respond that the "active ingredient" in both drug products was ALA. This shows that, for patent term extension purposes, the FDA views the "active ingredient" to be the particular salt or ester form actually found in the drug product, and not the "active moiety."

In sum, the PTO's argument that the FDA "consistently treated 'active ingredient' to mean 'active moiety'" when "active ingredient" is followed by the "including" clause (PTO Br. at 31) is simply wrong. If one was going to look to the FDA for guidance in interpreting the patent term extension statute, Photocure submits that it would make much more sense to look to how the FDA has interpreted the patent term extension statute itself, and not how it has interpreted the "marketing exclusivity" provisions.

For all of these reasons, this Court should not defer to the FDA's interpretation of the "marketing exclusivity" provisions.

2. The PTO's Reliance on the Legislative History Should Be Rejected

The PTO relies heavily on the legislative history to support its proposed statutory construction. In particular, the PTO argues that its interpretation of the statute is in line with Congress' intent to "reward *only* truly innovative research—involving 'new chemical entities ["NCEs"].'" (PTO Br. 31-32.) As an initial matter, we note that because the statutory language here has a plain meaning, the PTO "must provide 'an *extraordinary showing* of contrary intentions'" to overcome that plain meaning. *See Glaxo II*, 894 F.2d at 396 (*quoting Garcia v. United States*, 469 U.S. 70, 75 (1984)) (emphasis added by *Glaxo II* Court).

In *Glaxo II*, this Court rejected the PTO's reliance on the legislative history. *See Glaxo II*, 894 F.2d at 396-99. The Court, citing at least some of the same

Congressional report language relied on by the PTO (PTO Br. at 32), stated that "[t]he Commissioner argues that this language shows Congress' intent that 'product' was to mean 'new chemical entities' as defined by FDA. We are unpersuaded . . . we simply cannot find any clear statement that extensions are required based on first approval of 'new chemical entities.'" *Id.* at 397-98. Similarly, the district court in this case rejected the PTO's attempted reliance on the legislative history, stating that "the Court could find no legitimate support for the active moiety approach in the legislative history." (A16.) Indeed, even the PTO acknowledges that "the legislative history does not directly address the meaning of 'active ingredient.'" (PTO Br. at 31.)

3. The PTO's Argument That Photocure's Construction of the Statute Must Be Wrong Because It Leads to "Asymmetrical" Results Should Be Rejected

The PTO argues that Photocure's construction of the statute should be rejected because it leads to "asymmetrical" results – namely, if an ester is approved first and then the corresponding acid is approved, only the ester would support a patent term extension (because an ester of the active ingredient was previously approved), whereas if the acid is approved first and then the ester, both would support an extension. (PTO Br. at 16-17 and 33-34.) This argument should be rejected.

For one thing, Congress may have intended these "asymmetrical" results on the theory that it is more difficult to identify a new salt or ester of a previously-approved acid than it is to de-salify a previously-approved salt or de-esterify a previously-approved ester.[23] Thus, Congress may have believed that the former was worthy of a patent term extension, while the latter was not. As the district court stated in *Glaxo I* in rejecting this same argument:[24]

> [T]he 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. 1229 n. 12; *see also Abbott Labs. v. Young*, 920 F.2d 984, 993 (D.C. Cir. 1990) (Edwards, J., dissenting) ("Intuition suggests that a 'derivative' drug is likely to be invented *after* the 'parent' drug, rather than the other way around.").

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[23] For any given acid, there are many possible salts and esters, while for any given salt or ester, there is only one corresponding acid.

[24] The PTO has criticized this rationale because it was set forth in the *Glaxo I* opinion without any cited support. However, the PTO has not cited any support contradicting this rationale, or even asserted that this rationale is not logical. Since the PTO is the party asserting that the statute should not be given its plain meaning, the burden should be on the PTO to show why this explanation for the asymmetry is not correct.

In *Glaxo II*, this Court held that Congress may have intended the "asymmetrical" results,[25] particularly given that the Hatch-Waxman Act (like all legislation) was the product of compromise:

> We simply cannot say that the plain meaning of section 156 would provide unwanted results because Congress may very well have contemplated all the ramifications of its chosen definition in light of the political realities as seen played out in the legislative process, and we must assume it did.

894 F.2d at 397.

In any event, just as this Court held in *Glaxo II*, the alleged "asymmetrical" results should not override the plain meaning of the statute.

4. The PTO's Argument That Its Statutory Interpretation Is Entitled to *Skidmore* Deference Should Be Rejected

The PTO argues that it is entitled to *Skidmore* deference. (PTO Br. 35-37.) In *Skidmore*, the Court articulated the following standard for determining the degree to which "the rulings, interpretations and opinions" of an agency should guide the reviewing court: "The weight of such a judgment in a particular case will depend upon the thoroughness evident in its consideration, the validity of its reasoning, its consistency with earlier and later pronouncements, and all those

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[25] The Court's opinion in *Glaxo II* does not explicitly refer to the PTO's "asymmetrical" results argument. However, the opinion indicates that the PTO contended that "applying the plain meaning of section 156 to patent term extension determinations will create absurd results. . .", 894 F.2d at 396, and a review of the PTO's principal brief confirms that the "absurd results" it was (continued…)

factors which give it power to persuade." *See Skidmore v. Swift & Co.*, 323 U.S. 134, 140 (1944).

The district court held that the PTO's statutory interpretation was not entitled to *Skidmore* deference because – as the PTO acknowledged (A1014-15) – it was totally inconsistent with the section of the current Manual of Patent Examining Procedure regarding patent term extensions (A19), which states that

> A "drug product" means the active ingredient found in the final dosage form prior to administration of the product to the patient, not the resultant form the drug may take after administration. In this regard, a drug in the ester form which is used for oral administration is a different drug product from the same active moiety in a salt form which is administered by injection, even though both the salt and ester form are used to treat the same disease condition. The ester form is a different active ingredient from the salt form.

MPEP § 2751 (Eighth Ed., Rev. 7, July 2008) (A968.)

Thus, the district court concluded that the PTO was not entitled to deference for being "consistent" or "careful" in interpreting the patent term extension statute. (A19.) This conclusion is further supported by the PTO's inconsistent bases for rejecting Photocure's patent term extension application. (A519, A743.) Notably, in its final decision, the PTO held that the active ingredient in METVIXIA is ALA (A743), whereas in its initial decision, it held that the active ingredient in

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referring to was the "asymmetrical" results referred to here. *See Glaxo II*, Brief for the Appellant at 11, 18-19.

METVIXIA is MAL HCl (A519). No cogent explanation has been provided for these contradictory conclusions.[26]

Finally, this conclusion is supported by the PTO's grant of PTE's based on the approvals of drug products corresponding to the same active moiety as previously-approved drug products during the post-*Glaxo II*, pre-*Pfizer II* period. For example, the PTO granted a PTE based on the 1996 approval of the DAUNOXOME drug product, which contains daunorubicin citrate as the active ingredient, even though the CERUBIDINE drug product, which contains daunorubicin hydrochloride as the active ingredient, had been approved in 1995 (A972-84 at A982; A989-90).[27] Under the PTO's current interpretation of the statute, these PTE's would not have been granted.

The district court also concluded that the PTO's construction was not entitled to *Skidmore* deference because it "runs afoul of the plain meaning of the statute and finds no legitimate support in the legislative history," and thus "is not

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[26] Such an unexplained inconsistency may be the basis for holding that agency action is arbitrary and capricious. *See National Cable & Telecommunications Assoc. v. Brand X Internet Services*, 545 U.S. 967, 981 (2005). Another example of this inconsistency is the PTO's initial decision in another case indicating that *Pfizer II* overruled *Glaxo II* (A855), and its subsequent repudiation of that legally untenable position. (A911.)

[27] The PTO also granted a PTE based on the 1996 approval of the ETOPOPHOS drug product (A972), which contains etoposide phosphate as the active ingredient, even though the VEPESID drug product, which contains etoposide as the active ingredient, had been approved in 1983.

reasonable." (A19.) For all of the reasons given above, this is correct, and thus the PTO is not entitled to *Skidmore* deference for this reason as well. *See Eldredge v. Dep't of the Interior*, 451 F.3d 1337, 1343 (Fed. Cir. 2006) (*Skidmore* deference not warranted where to defer would "adopt such a counter intuitive reading of the statute").

CONCLUSION

For the foregoing reasons, the district court's decision should be affirmed. This case should be remanded to the PTO for further action consistent with that decision.

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DATED: August 4, 2009

PROOF OF SERVICE

I, John W. Bateman, hereby certify that on this 4th day of August, 2009, I caused two (2) copies of the foregoing BRIEF FOR PLAINTIFF-APPELLEE PHOTOCURE ASA to be served via overnight delivery and electronic mail upon:

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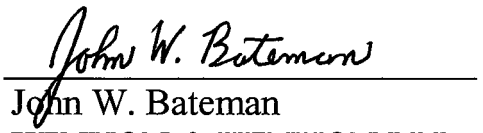
I , John W. Bateman, also hereby certify that on this 4th day of August, 2009, I caused the original and twelve (12) copies of the foregoing BRIEF FOR PLAINTIFF-APPELLEE PHOTOCURE ASA to be filed with the Clerk of the Court via hand delivery.



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CERTIFICATE OF COMPLIANCE

The undersigned hereby certifies that this brief complies with the type-volume limitation of Fed. R. App. P. 32(a)(7)(B)(i). The brief was prepared using Microsoft Word 2003, using a proportional 14-point typeface and contains 13,013 words. As permitted by Fed. R. App. P. 32(a)(7)(C), the undersigned has relied upon the word count of this word-processing system.

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