IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: U.S. Reissue Patent No. 41,571
Issued: August 24, 2010
Inventors: Robert F. Reder, Paul D. Goldenheim, and Robert F. Kaiko
For: **Method of Providing Sustained Analgesia with Buprenorphine**

Attorney Docket No: Y2428-00178
SKGF Docket No: 1861.3000000/JMC/THN

Transmittal Letter

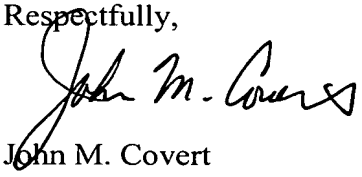
Attn: Mail Stop HATCH-WAXMAN PTE

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Sir:

Transmitted herewith is a Communication regarding an Application for Extension of Patent Term Under 35 U.S.C. § 156 for U.S. Reissue Patent No. RE41,571, accompanied by a copy of the PTO's communication. The Director is hereby authorized to charge all required extension of time fees to our Deposit Account No. 19-0036, if such fees are not otherwise provided for in such reply.

On behalf of Purdue Pharma L.P.,
Respectfully,



John M. Covert
Attorney for Applicant
USPTO Registration No. 38,759
Sterne, Kessler, Goldstein & Fox PLLC
1100 New York Avenue
Washington, D.C. 20005

Date: November 4, 2011

JOHN M. COVERT
DIRECTOR
(202) 772-8673
JCOVERT@SKGF.COM

Sterne Kessler Goldstein Fox
ATTORNEYS AT LAW

November 4, 2011

Beverly Friedman
Office of Regulatory Policy
FOOD AND DRUG ADMINISTRATION
10903 New Hampshire Ave., Bldg. 51, Rm. 6222
Silver Spring, Maryland 20993-0002

Mary C. Till
Senior Legal Advisor
Office of Patent Legal Administration
OFFICE OF THE DEPUTY COMMISSIONER FOR PATENT POLICY UNITED STATES PATENT AND TRADEMARK OFFICE
P.O. Box 1450
Alexandria, Virginia 22313-1450

Re: Application for Extension of Patent Term Under 35 U.S.C. § 156 for U.S. Reissue Patent No. RE41,571
Our Ref.: 1861.3000000/JMC/THN

This letter addresses the October 12, 2011 non-final determination by the Offices of Patent Legal Administration and Deputy Commissioner for Patent Examination Policy of the United States Patent and Trademark Office ("PTO") that U.S. Reissue Patent No. RE41,571 (the "'571 patent") would *not* be eligible for extension under 35 U.S.C. § 156 for the alleged failure to comply with the requirements of § 156(a)(5)(A) (copy enclosed). As set forth below, this initial determination is erroneous as it is contrary to the relevant provisions of the statute, as well as recent Federal Circuit precedent interpreting such provisions.

By way of background, Purdue Pharma L.P. is the owner of record of the '571 patent, one of several patents covering Purdue's buprenorphine transdermal formulation product marketed under the trade name Butrans®. The first opioid analgesic intended to be worn for seven days, Butrans® is indicated for the management of moderate to severe chronic pain in patients requiring a continuous, around-the-clock opioid analgesic for an extended period of time. Since its launch in January 2011, Butrans® has been commercially successful in the United States (and has had similar commercial success in a number of other countries, under the trade names Butrans®, BuTrans®, Norspan®, Restiva®, Sovenor®, and Buvalor®). The domestic launch of Butrans® was made possible only after a full and rigorous regulatory review was conducted pursuant to Section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (codified as 21 U.S.C. § 355(b)(1)) which required, *inter alia*, full reports of investigations showing safety and efficacy of use. The regulatory review period for Butrans® lasted *over ten years*, whereupon

FDA approved Purdue's NDA No. 21-306 for the 5, 10, and 20 mcg/hr dosage strengths of Butrans® on June 30, 2010.

After obtaining approval of NDA No. 21-306, Purdue timely filed an application for extension of patent term under 35 U.S.C. § 156 on August 26, 2010, within the sixty-day time period for filing such application. 35 U.S.C. § 156(d)(1). On October 12, 2011, the PTO sent a letter to FDA seeking confirmation of: (1) whether Butrans® has been subject to a regulatory review period within the meaning of 35 U.S.C. § 156(g) before its *first* commercial marketing or use; and (2) whether the application for patent term extension was filed within the sixty-day period as required by 35 U.S.C. § 156(d)(1). The PTO further noted that the "issue here is whether the approval of buprenorphine in BUTRANS is the first permitted commercial marketing or use as required by § 156(a)(5)(A)."1 The answer to all questions is affirmative for at least the following reasons:

First, Butrans® represents the first permitted commercial marketing or use under the meaning of § 156(a)(5)(A) based on its active ingredient. For purposes of satisfying § 156(a)(5)(A), "product" means "[a] drug product," which in turn means "the active ingredient of . . . a new drug . . . including any salt or ester of the active ingredient, as a single entity or in combination with another active ingredient." 35 U.S.C. § 156(f). Because Butrans® is the first product approved containing as its active ingredient buprenorphine *base*, as opposed to prior products approved containing buprenorphine *hydrochloride*,2 it is the first product permitted for commercial marketing or use under the meaning of § 156(a)(5)(A). There is no dispute as to whether Butrans® has undergone a full regulatory review period ending in FDA's approval of NDA No. 21-306 on June 30, 2010.

* * *

Second, the PTO's initial determination is contrary to recent precedent by the United States Court of Appeals for the Federal Circuit in *Photocure ASA v. Kappos*, 603 F.3d 1372 (Fed. Cir. 2010) and *Ortho-McNeil Pharm., Inc. v. Lupin Pharm., Inc.*, 603 F.3d 1377 (Fed. Cir. 2010).

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1 35 U.S.C. § 156(a)(5)(A) provides: 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: . . . 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* (emphasis added).

2 Examples of prior approved products containing buprenorphine hydrochloride include: (1) Buprenex® (NDA No. 18-401; injectable buprenorphine hydrochloride solution); (2) Subutex® (NDA No. 20-732; buprenorphine hydrochloride sublingual tablet); and (3) Suboxone® (NDA No. 20-733; buprenorphine hydrochloride and naloxone hydrochloride sublingual tablet).

In *Photocure*, the Federal Circuit affirmed the district court's ruling that the PTO's decision to deny Photocure's application for patent term extension under § 156 was "'not in accordance with law,' and that the patent on MAL hydrochloride is subject to term extension." 603 F.3d at 1373-74. The PTO had found that MAL hydrochloride is the same product as ALA hydrochloride, which had previously received FDA approval for the same therapeutic use (treatment of precancerous cell growths on the skin) and therefore was not the first commercial marketing or use of that "product." *Id.* at 1375. The district court disagreed, holding that MAL hydrochloride, the methyl ester of ALA hydrochloride, is the active ingredient of a new drug product that was subject to a full regulatory review period before commercial marketing and use was permitted. The Federal Circuit affirmed. The Court concluded that "MAL hydrochloride is the active ingredient of a new and improved drug product" (*id.* at 1376), and found persuasive that:

> MAL hydrochloride is a different chemical compound from ALA hydrochloride, and it is not disputed that they differ in their biological properties, warranting separate patenting and separate regulatory approval, although their chemical structure is similar (*id.* at 1375).

As with MAL hydrochloride, buprenorphine base, the active ingredient of Butrans®, is a different chemical compound from its hydrochloride counterpart, imparting different pharmacological properties (including its ability to be absorbed through the transdermal route of administration), and thereby requiring it to undergo a separate full regulatory review period by FDA.

At the same time, the Federal Circuit in *Ortho-McNeil* affirmed a district court ruling that the patent on the antimicrobial compound levofloxacin, the levorotatory enantiomer of the racemate of ofloxacin (a previously-approved antimicrobial product), was entitled to patent term extension because levofloxacin is a different drug product from ofloxacin.3 603 F.3d at 1381. The Court acknowledged that "[a]lthough *enantiomers and their racemates have the same chemical composition, they differ in their physical, chemical, or biological properties*," and that the inventors of the patent covering levofloxacin determined that this compound "has properties that are significantly superior to those of ofloxacin." *Id.* at 1378 (emphasis added). The Court agreed with Ortho's argument that "an enantiomer has consistently been recognized, by FDA and the PTO, as a different 'drug product' from its racemate." *Id.* Finally, the Court noted that levofloxacin was on the one hand, viewed by FDA as a product requiring a full regulatory

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3 The Federal Circuit acknowledged that:

> A racemate consists of equal amounts of spatial isomers called enantiomers, molecules that are mirror images of each other. Due to their special orientation, enantiomers are optically active and are characterized by whether they rotate plane-polarized light clockwise (dextrorotatory) or counterclockwise (levorotatory).

Ortho-McNeil, 603 F.3d at 1378.

approval, and on the other, viewed by the PTO as separately patentable. *Id.* The Federal Circuit found no basis to challenge "these established FDA and PTO practices." *Id.*

This recent pair of cases illustrates how the Federal Circuit has specifically rejected the PTO's erroneous two-prong approach in determining whether a particular product represents the first permitted commercial marketing or use under the meaning of § 156(a)(5)(A) based on its active ingredient.4 The PTO's analysis of *Hoechst-Roussel Pharm., Inc. v. Lehman*, 109 F.3d 756 (Fed. Cir. 1997), *Glaxo Operations UK Ltd. v. Quigg*, 706 F.Supp. 1224 (E.D. Va 1989) (*Glaxo I*), and *Glaxo Operations UK Ltd. v. Quigg*, 894 F.2d 392 (Fed. Cir. 1990) (*Glaxo II*), used to support its conclusion of ineligibility of patent term extension of the '571 patent, is unavailing. To the contrary, the *Hoechst* and *Glaxo II* cases were both discussed in the Federal Circuit's *Photocure* opinion, the very opinion wherein it deemed the PTO's statutory interpretation of "active ingredient" to be "incorrect" – such term does not mean only the "active moiety" of the product (*i.e.*, the part responsible for the drug's pharmacological properties), but the product that is present in the *approved drug*. *Photocure*, 603 F.3d at 1375-76. Here, in the case of Butrans®, the focus should be placed on the active ingredient as it is found in the approved product, *i.e.*, buprenorphine base, as opposed to any buprenorphine active moiety that may have been previously approved, such as buprenorphine hydrochloride contained in other prior approved products (*e.g.*, Buprenex®, Subutex®, and Suboxone®).

* * *

Third, the PTO must follow the Federal Circuit's interpretation of the statute. As the Board of Patent Appeals and Interferences underscored in *Ex Parte Holt*:

> We take this occasion to explain what precedents are considered binding in proceedings in the Patent and Trademark Office (PTO). Where the Court of Appeals for the Federal Circuit has addressed a point of law in a published opinion, the Federal Circuit's decision is controlling.

1991 WL 326550 at *3 (B.P.A.I. 1991) (citations omitted). As in *Holt*, where the Federal Circuit has published an opinion interpreting §156(a)(5)(A) as to what constitutes a first commercial marketing or use of a product – in this case, buprenorphine base, the active ingredient of Butrans® – the PTO must follow the Federal Circuit's binding decisions in *Photocure* and

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4 In the October 12, 2011 letter, the PTO stated: "Applying the *Hoeschet* [*sic*] and *Glaxo* I analyses here, the active ingredient of BUTRANS® is buprenorphine. The question to ask is what substance is physically present in the product; here, it is buprenorphine. The next step to ask is whether any salt or ester of buprenorphine has been previously approved by FDA. Because a salt of buprenorphine, buprenorphine hydrochloride, has been approved first, before the approval of BUTRANS®, the grant of permission to commercially market or use BUTRANS® is NOT the first permitted commercial marketing or use of the product/active ingredient as required by Section 156(a)(5)(A) in light of the approvals of Buprenex, Subutex and Suboxone." October 12, 2011 PTO letter to FDA at 4.

Ortho-McNeil. The PTO's attempt to distinguish *Photocure* on the basis that the Federal Circuit used "non-statutory criteria" (*see* October 12, 2011 letter at 3) to reach its holding is unfounded and contrary to *Holt*.

* * *

Finally, the application was filed in a timely manner, on August 26, 2010, within sixty days after FDA's June 30, 2010 approval of NDA No. 21-306.

* * *

In summary, Butrans® represents the first commercial marketing and use of the active ingredient buprenorphine base and which has been subject to a full regulatory review period by FDA. As set forth above and more fully in Purdue's application, extension of patent term for the '571 patent is warranted.

On behalf of Purdue Pharma L.P.,
Respectfully,

John M. Covert
Attorney for Applicant
USPTO Registration No. 38,759
Sterne, Kessler, Goldstein & Fox PLLC
1100 New York Avenue
Washington, D.C. 20005

Enclosure

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UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

OCT 12 2011

Office of Regulatory Policy
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 51, Rm. 6222
Silver Spring, MD 20993-0002

Attention: Beverly Friedman

The attached application for patent term extension of U.S. Patent No. RE41571 was filed on August 26, 2010, under 35 U.S.C. § 156 relating to NDA# 21-306 for the human drug BUTRANS® (buprenorphine).

The assistance of your Office is requested in determining whether the product identified in the application, BUTRANS® (buprenorphine), has been subject to a regulatory review period within the meaning of 35 U.S.C. § 156(g) before its **first** commercial marketing or use. Our analysis regarding compliance with 35 U.S.C. § 156(a)(5)(A) follows below. Additionally, we request that you confirm the approval date of June 30, 2010, so that USPTO can determine whether the application for patent term extension was filed within the sixty-day period as required by 35 U.S.C. § 156(d)(1).

Since a determination has not been made whether the patent in question claims a product which has been subject to the Federal Food, Drug and Cosmetic Act, or a method of manufacturing or use of such a product, this communication is NOT to be considered as notice which may be made in the future pursuant to 35 U.S.C. § 156(d)(2)(A).

Our review of the application to date indicates that the subject patent would NOT be eligible for extension of the patent term under 35 U.S.C. § 156 as failing to comply with the requirements of 35 U.S.C. § 156(a)(5)(A).

The approved product of NDA No. 21-306 is BUTRANS®, having as the active ingredient, buprenorphine. Applicant notes that buprenorphine has not itself been previously approved. Applicant also notes that a salt of buprenorphine, buprenorphine hydrochloride, has been approved prior to the approval of BUTRANS® in the drug products Buprenex (approved in 1981), Subutex (approved in 2002) and Suboxone (approved in 2002).

At issue here is whether the approval of buprenorphine in BUTRANS is the first permitted commercial marketing or use as required by § 156(a)(5)(A). In order to comply with § 156(a)(5)(A), the approval of the "product" must be the first permitted commercial marketing or use. Section 156(f) defines products as "drug product" which in turn is defined as "the active ingredient . . . including any salt or ester of the active ingredient. . . ." Thus, the inquiry to ascertain compliance with § 156(a)(5)(A) would require determining whether the permission for the commercial marketing or use of the active ingredient, or a salt of the active ingredient or an ester of the active ingredient, was the first permitted commercial marketing or use. Here, a salt

of the active ingredient, buprenorphine hydrochloride, was the first permitted commercial marketing or use of the "product" as that term is defined in § 156(f). Thus, based on a plain reading of the statute, the approval of BUTRANS® does not comply with § 156(a)(5)(A).

In addition to the statutory analysis, the issue of compliance with 35 U.S.C. § 156(a)(5)(A) was squarely addressed by the Federal Circuit in *Photocure v. Kappos*, 603 F.3d 1372 (Fed. Cir. 2010), where the court relied on its previous decision in *Glaxo v. Quigg*, 894 F.2d 392 (Fed. Cir. 1990) (*Glaxo II*), for its determination of eligibility of a patent for extension based on the regulatory review of Photocure's Metvixia product. Specifically, the Federal Circuit in *Photocure* stated that "[i]n *Glaxo* this court held that 'product' in §156(a) means the product that is present in the drug for which federal approval was obtained," Id. at 1376 (citing to *Glaxo II* at 894 F.2d at 393–95). Thus, *Glaxo II* is highly instructive in determining when a patent claiming an active ingredient, which may contain the same active moiety as a previously approved active ingredient, is eligible for extension.

In *Glaxo II*, the Federal Circuit affirmed the district court's determination that a patent which claimed an ester of cefuroxime was eligible for extension regardless of previous approvals of two salts of cefuroxime. *Glaxo II* at 393. Although the *Glaxo II* court did not explicitly set forth its rationale for determining that the patent was eligible for extension under section 156, in affirming the district court, the Federal Circuit implicitly adopted the district court's rationale. There, the district court in *Glaxo v. Quigg*, 706 F. Supp 1224 (E.D. Va. 1989) (*Glaxo I*) framed the rationale for eligibility as:

> the question sharply presented is whether the "product" referred to in (a)(5)(A) is cefuroxime axetil, on the one hand, or cefuroxime, the parent acid on the other. The answer to this question turns on the statutory definition of "product." Subsection (f) of Section 156 defines "product" as "a drug product," which, in turn, is defined as follows:
>
> > (2) The term "drug product" means the active ingredient of 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.
>
> 35 U.S.C. § 156(f)(2).
>
> The central question then is whether the active ingredient of Ceftin Tablets is the ester cefuroxime axetil or the parent acid cefuroxime. If the former is true, plaintiff is entitled to an extension of its patent term. If the latter is true, then no extension would be warranted because the FDA has previously approved NDA's for Zinacef and Kefurox, two sodium salts of cefuroxime.

Glaxo I at 1227.

Additionally, the *Photocure* court pointed out that they held in *Hoechst-Roussel Pharms., Inc. v. Lehman*, 109 F.3d 756, 759 (Fed. Cir. 1997) that "[f]or purposes of patent term extension, this

active ingredient must be present in the drug product when administered." *Photocure* at 1376. Thus, the active ingredient of Photocure's Metvixia product is methylaminolevulinate hydrochloride, because that is the substance physically present in the final dosage form.

Applying the *Hoeschet* and *Glaxo I* analyses here, the active ingredient of BUTRANS® is buprenorphine. The question to ask is what substance is physically present in the product; here, it is burprenorphine. The next step is to ask whether any salt or ester of buprenorphine has been previously approved by FDA. Because a salt of buprenorphine, buprenorphine hydrochloride, has been approved first, before the approval of BUTRANS®, the grant of permission to commercially market or use BUTRANS® is NOT the first permitted commercial marketing or use of the product/active ingredient as required by section 156(a)(5)(A) in light of the approvals of Buprenex, Subutex and Suboxone. Accordingly, the '571 patent is ineligible for extension under the provisions of section 156.

Notwithstanding the statutory requirements, the comments of the *Photocure* court serve to buttress the conclusion that the approvalof Metvixia complied with § 156(a)(5)(A), but did not provide additional criteria to confer eligibility. Applicant attempts to garner support for an extension for BUTRANS® by analogizing the present extension application with Photocure's extension application with regard to non-statutory criteria as discussed in *Photocure*. Specifically, Applicant states that even though a salt of BUTRANS® had been previously approved, the decision in *Photocure* would indicate that the previous approval of buprenorphine hydrochloride does not bar extension of a patent claiming BUTRANS®. Applicant points to the *Photocure* opinion where it is stated that Metvixia is eligible for extension because Metvixia had different biological properties and underwent separate regulatory approval. While true that the *Photocure* court discussed different biological properties, nothing in section 156 requires analyzing biological properties to determine eligibility. Additionally, any "new drug," as defined in 21 U.S.C. § 321(p), must undergo separate regulatory approval as per 21 U.S.C. § 355 (no person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed pursuant to subsection (b) or (j) is effective with respect to such drug). Since the additional circumstances discussed by the *Photocure* court in finding that the approval of Metvixia could support an extension of Photocure's patent are not statutory requirements, alleging similar circumstances fails to confer eligibility here.

Inquiries regarding this communication should be directed to the undersigned at (571) 272-7755 (telephone) or (571) 273-7755 (facsimile).

Mary C. Till
Senior Legal Advisor
Office of Patent Legal Administration
Office of the Deputy Commissioner
for Patent Examination Policy

cc: John M. Covert
Sterne, Kessler, Goldstein & Fox PLLC
1100 New York Ave.
Washington, DC 20005