TO:	Troxyca (Oxycodone Hydrochloride and Naltrexone Hydrochloride) ER capsules (new drug application (NDA) 207621)
FROM:	Emily Helms Williams KHR for EHW 8/19/16 Regulatory Counsel Office of Regulatory Policy (ORP)
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THROUGH:	Carol Bennett 8/A/16 Deputy Director, ORP
	Sharon Hertz, MD Division Director, DAAAP
DATE:	August 19, 2016
RE:	Citizen Petition from Purdue Pharma L.P. (FDA-2015-P-5108)

A citizen petition was submitted on behalf of Purdue Pharma L.P. (Purdue), dated and received on December 22, 2015 (Petition). That Petition was subject to section 505(q) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), which requires FDA to take final Agency action within 150 days of submission. On May 20, 2016, FDA denied the Petition without comment on the Petition's specific requests, because Pfizer Inc.'s (Pfizer) 505(b)(2) application for ALO-02 (Troxyca ER; oxycodone hydrochloride and naltrexone hydrochloride), which is the subject of the Petition, was pending before the Agency and DAAAP's review was not complete. DAAAP is now completing its review of Pfizer's Troxyca application (NDA 207621). ORP, DAAAP, and other components of the Agency have considered the issues raised in the Petition as they relate to the application. This memorandum documents consideration of the issues.

In the Petition, Purdue states that Pfizer, Inc. (Pfizer) submitted a new drug application (NDA) under section 505(b)(2) of the FD&C Act (21 U.S.C. 355(b)(2)) for ALO-02,[1] a "twice-a-day

[1] The Petition refers to the drug product at issue as "ALO-02." As discussed further below, the proprietary name for the product referred to in the Petition is Troxyca ER. We use the proprietary name for the drug product in this memorandum except when discussing the Petition's requests or quoting from the Petition.

OxyContin, disruption of the tablet and controlled-release mechanism for abuse or misuse "'can lead to rapid release and absorption of a potentially fatal dose of oxycodone.'" 78 FR 23273 (April 18, 2013) (quoting the Original OxyContin labeling).

Purdue reformulated the product with physicochemical properties intended to make the tablet more difficult to manipulate for purposes of abuse or misuse and submitted a new application for oxycodone HCl controlled-release tablets (NDA 022272) in November 2007. In April 2010, the Agency approved Reformulated OxyContin, which was submitted under section 505(b)(1) of the FD&C Act, with dosage strengths of 10, 15, 20, 30, 40, 60, and 80 mg (hereafter referred to as Reformulated OxyContin). Reformulated OxyContin is indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. Several patents for Reformulated OxyContin are listed in the Orange Book.

In correspondence dated August 10, 2010, Purdue notified FDA that it had ceased shipment of Original OxyContin, and FDA subsequently moved Original OxyContin to the "Discontinued Drug Product List" (Discontinued) section of the Orange Book. In April 2013, FDA approved a supplemental application for Reformulated OxyContin, approving changes to the product labeling that describe certain abuse-deterrent properties of the reformulated product. Shortly after, FDA announced in a Federal Register notice its determination that Original OxyContin was withdrawn from sale for reasons of safety or effectiveness because, although it had the same therapeutic benefits as Reformulated OxyContin, it posed an increased potential for abuse by certain routes of administration, when compared to Reformulated OxyContin. 78 FR 23273 (April 18, 2013). Therefore, based on the totality of the data and information available to the Agency at the time, FDA concluded that the benefits of Original OxyContin no longer outweighed its risks. 78 FR 23274. In that Federal Register notice, FDA also stated that the Agency will remove Original OxyContin from the list of products published in the Orange Book, and it subsequently did so. 78 FR 23275. Purdue voluntarily requested that approval of the application for Original OxyContin be withdrawn and waived its opportunity for a hearing. FDA withdrew approval of the application under section 505(e) of the FD&C Act in August 2013. 78 FR 48177 (Aug. 7, 2013).

B. Targiniq ER

In July 2014, the Agency approved NDA 205777 for Targiniq ER (oxycodone HCl and naloxone HCl extended-release tablets) in dosage strengths of 10 mg/5 mg, 20 mg/10 mg, and 40 mg/20 mg, which was submitted under the pathway described in section 505(b)(2) of the FD&C Act (a 505(b)(2) NDA). Purdue holds NDA 205777. The Targiniq ER NDA cited Narcan (naloxone hydrochloride; NDA 16636) as the listed drug[3] relied upon and cross-referenced Purdue's NDAs for Original OxyContin and Reformulated OxyContin. Targiniq ER is indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. Targiniq ER has pharmacologic properties that are expected to reduce abuse by the intranasal and intravenous

[3] See 21 CFR 314.3 (defining listed drug).

oral routes of administration. Several patents for Embeda are listed in the Orange Book.

II. LEGAL FRAMEWORK

A. 505(b)(2) NDAs

Section 505(b)(2) of the FD&C Act was enacted as part of the Drug Price Competition and Patent Term Restoration Act of 1984, Public Law 98-417 (the Hatch-Waxman Amendments). The Hatch-Waxman Amendments reflect Congress's efforts to balance the need to "make available more low-cost generic drugs by establishing a generic drug approval procedure for pioneer drugs first approved after 1962" with new incentives for drug development in the form of marketing exclusivity and patent term extensions.[4]

Section 505(b)(2) of the FD&C Act describes an application that contains full reports of investigations of safety and effectiveness, where at least some of the information relied upon by the applicant for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use (e.g., published literature and/or the Agency's finding of safety and/or effectiveness for one or more listed drugs). When a 505(b)(2) applicant seeks to rely on a finding of safety and effectiveness for a previously approved drug product (i.e., a listed drug), the applicant must establish that its basis for relying on a previous approval is scientifically justified. A 505(b)(2) applicant can bridge[5] its proposed product to the previously approved product by submitting, for example, studies that measure the relative bioavailability[6] of the two products or other appropriate scientific information. A 505(b)(2) applicant may rely on FDA's finding of safety and effectiveness for a listed drug only to the extent that the proposed product in the 505(b)(2) application shares characteristics (e.g., active ingredient, dosage form, route of administration, strength, indication, conditions of use) in common with the listed drug(s). The 505(b)(2) application must include sufficient data to support any differences between the proposed drug and the listed drug(s) and demonstrate that the proposed drug product meets the statutory approval standard for safety and effectiveness. The 505(b)(2) pathway permits sponsors to rely on what is already known about a drug, thereby avoiding unnecessary duplication of human or animal studies and conserving resources.

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[4] See House Report No. 98-857, part 1, at 14-15 (1984), reprinted in 1984 U.S.C.C.A.N. 2647 at 2647-2648.

[5] A *bridge* in a 505(b)(2) NDA is information to demonstrate sufficient similarity between the proposed product and the listed drug, or between the proposed product and a product described in published literature, to justify reliance scientifically on certain existing information for approval of the 505(b)(2) NDA. See also FDA draft guidance for industry Applications Covered by Section 505(b)(2) (Draft 505(b)(2) Guidance) at 8-9, available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. We update guidances periodically. The most recent versions of guidances are available on the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. When final, this guidance will represent the FDA's current thinking on this topic.

[6] Bioavailability data provide an estimate of the fraction of the drug absorbed, as well as provide information related to the pharmacokinetics of the drug. See, e.g., FDA's guidance for industry entitled "Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs - General Considerations," at 3.

FDA is required to publish the patent information provided by the NDA holder for drugs approved under 505(c) and does so in the Orange Book (section 505(b)(1), (c)(2), and (j)(7) of the FD&C Act, and 21 CFR 314.53(e)).

For each unexpired patent listed in the Orange Book for a listed drug it references, the 505(b)(2) applicant must submit either a paragraph III certification (delaying approval until the date on which such patent will expire), a paragraph IV certification (certifying that such patent is invalid or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted), or, with respect to a method of use patent, a statement that the patent does not claim a use for which the applicant is seeking approval and for which information is required to be filed under section 505(b) and (c) of the FD&C Act (section 505(b)(2)(A) and (B) of the FD&C Act).[13, 14] The applicant is not required to certify to all patents "for every drug containing the same active ingredient that relied in part on the same underlying investigations on which the 505(b)(2) applicant seeks to rely."[15] Rather, the applicant's patent certification obligations are limited to those patents that claim the *specific listed drug* upon which the applicant has relied for FDA's finding of safety and effectiveness to support the approval of the 505(b)(2) NDA.[16]

A 505(b)(2) applicant submitting a paragraph IV certification to a listed patent must provide the NDA holder for the listed drug(s) and each patent owner with notice of its patent certification, including a description of the legal and factual basis for its assertion that the patent is invalid or will not be infringed (section 505(b)(3) of the FD&C Act).[17] Should the NDA holder or patent owner initiate a patent infringement action against the 505(b)(2) applicant within 45 days of receiving the required notice, approval of the 505(b)(2) NDA generally will be stayed for 30 months from the date of receipt of the notice, unless a court orders otherwise (section 505(c)(3)(C) of the FD&C Act).[18] This process may permit resolution of patent infringement issues before the product described in the 505(b)(2) NDA is approved and marketed.

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[13] A 505(b)(2) applicant may also submit a paragraph I certification (that such patent information has not been filed) or paragraph II certification (that such patent has expired).

[14] See also, e.g., 21 CFR 314.50(i)(1) and 21 CFR 314.53 (FDA regulations implementing patent listing and certification provisions).

[15] FDA Response to Abbott Laboratories and Laboratoires Fournier (November 30, 2004) (Docket No. FDA-2004-P-0089) (previously Docket No. 2004P-0386) (Fenofibrate Petition Response) at 6 (emphasis added).

[16] See Takeda Pharmaceuticals, U.S.A., Inc. v. Burwell, 2015 U.S. Dist. LEXIS 5908 (D.D.C. Jan. 13, 2015) (holding that the applicant need only certify to the product patents or the method-of-use patents that are associated with the reference listed drug (i.e., the drug product on whose finding of safety or effectiveness the 505(b)(2) applicant relies)), *affirmed*, No. 15-5021 (D.C. Cir. July 15, 2016).

[17] See e.g., 21 CFR 314.52.

[18] See e.g., 21 CFR 314.107.

B. The Petition Arguments Lack Merit

In support of its two requests, the Petition raises the following three arguments:

(1) That Pfizer must reference Reformulated OxyContin in its 505(b)(2) NDA for ALO-02 because a comparative study with OxyContin that Pfizer conducted in 2012 was included by Pfizer in its pending NDA for ALO-02;

(2) That because Pfizer relies upon the listed drug Roxicodone IR in its 505(b)(2) NDA for ALO-02, the application must reference OxyContin as well; and

(3) That Pfizer must reference Targiniq ER in its 505(b)(2) NDA for ALO-02 because Targiniq ER is the "most similar listed drug" to ALO-02.

These arguments are addressed in turn below.

1. Pfizer's Study Using Troxyca ER and Reformulated OxyContin

The Petition states that, in 2012, Pfizer conducted a study comparing the pharmacokinetics (PK), safety, and tolerability of ALO-02 (40 mg twice daily (BID) and 80 mg once daily (QD)) and Reformulated OxyContin (40 mg BID), and that Pfizer acknowledged including the study in its pending NDA. Petition at 10. The Petition cites one published article authored by Pfizer;[22] and states that the published version of the article includes certain comparisons between the ALO-02 arms and Reformulated OxyContin, and that, based on the comparisons with Reformulated OxyContin, the authors conclude that ALO-02 is suitable for administration around the clock to treat chronic pain. Petition at 12. The Petition states that the study's showing that ALO-02 and Reformulated OxyContin have similar safety and tolerability, and are comparable on relevant PK parameters (despite certain differences) constitutes a "direct bridge" between ALO-02 and the findings of safety and efficacy for Reformulated OxyContin. Id. at 12. According to the Petition, because of this direct comparison, Pfizer must reference Reformulated OxyContin in its 505(b)(2) NDA and certify to the patents listed in NDA 022272.

FDA Response

Pfizer conducted a study using Troxyca ER and Reformulated OxyContin[23] in 2012, and that study was submitted in Pfizer's 505(b)(2) NDA for Troxyca ER. This study was an open-label, single- and multiple-dose, cross-over, pharmacokinetic study comparing Troxyca ER 40 mg/4.8

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[22] Gandelman et. al, Single- and Multiple-Dose Study to Evaluate Pharmacokinetics, Safety and Tolerability in Healthy Volunteers: A Comparison of Extended-Release Oxycodone With Sequestered Naltrexone 40 mg Twice Daily to OxyContin 40 mg Twice Daily and Extended-Release Oxycodone With Sequestered Naltrexone 80 mg Once Daily. Clinical Pharmacology in Drug Development 4:361-369 (2015).

[23] The study does not specify whether it used Original OxyContin or Reformulated OxyContin. Given that the study was conducted in 2012, after Original OxyContin was discontinued in 2010, and the study states that the OxyContin at issue was obtained commercially, we believe it used Reformulated OxyContin.

> NDA relied on, as well as to the patents of any underlying NDA on which that approved 505(b)(2) NDA relied for approval. This is analogous to the requirement that an ANDA applicant referencing an approved suitability petition (or another ANDA approved pursuant to a suitability petition) certify to the patents for the approved NDA upon which the suitability petition or ANDA approval was based.[25]

FDA Response

The FD&C Act together with the implementing regulations require a patent certification by the pending 505(b)(2) applicant only with respect to patents that are listed for the drug product on whose finding of safety and effectiveness the applicant relies. Thus, when a pending 505(b)(2) NDA relies for approval on a different sponsor's previously-approved 505(b)(2) NDA, the pending 505(b)(2) applicant is required only to certify to patents of the listed drug that it relies on.[26] FDA does not require the sponsor of the pending 505(b)(2) NDA to certify to patents that a different sponsor's previously-approved listed drug may, itself, have relied on when seeking its initial approval.[27]

As a result, Pfizer was not required to cite and certify to patents for any listed drug that Roxicodone relied upon for approval. Although the footnote text Purdue cited appears in the Fenofibrate Petition Response, the Agency's response addressed different facts and circumstances; and the issue implicated by the footnote was not squarely before the Agency.[28]

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[25] Fenofibrate Petition Response at 10, note 14.

[26] See e.g., Fenofibrate Petition Response at 6 (stating that the language of section 505(b)(2) of the FD&C Act explicitly links the drug relied on for approval to the drug for which patent certifications must be made); Takeda Pharmaceuticals, U.S.A., Inc. v. Burwell, 2015 U.S. Dist. LEXIS 5908 (D.D.C. Jan. 13, 2015) (holding that the applicant need only certify to the product patents or the method-of-use patents that are associated with the reference listed drug (i.e., the drug product on whose finding of safety and effectiveness the 505(b)(2) applicant relies)), *affirmed*, No. 15-5021 (D.C. Cir. July 15, 2016).

[27] Similarly, FDA's regulations require sponsors to certify only to patents for the listed drug upon which the applicant relies. See 21 CFR 314.50(1)(i) (requiring certification to patents for the drug relied on that are listed pursuant to 21 CFR 314.53, i.e., patents in the Orange Book). Absent this limitation, it could be unmanageable for sponsors to determine which of many possible generations of patents would need to be certified to when submitting a 505(b)(2) NDA.

[28] Id. at 1. In the Fenofibrate Petition Response, the Agency addressed, and denied, the petitioner's request that a 505(b)(2) applicant must certify to patents on all later-approved products that were approved based, in part, on some or all of the same underlying investigations as the listed drug relied upon. In a more recent citizen petition response, the Agency acknowledged that the Fenofibrate Petition did not raise the issue discussed in the cited footnote and provided additional clarification regarding the footnote text as follows:

> [A]lthough we noted in the Fenofibrate Petition Response that a 505(b)(2) applicant seeking approval for a drug product that relies upon FDA's finding of safety and/or effectiveness for a drug product approved through the 505(b)(2) pathway "*should* certify to the patents of the 505(b)(2) NDA relied on, as well as to the patents of any underlying NDA on which that approved 505(b)(2) NDA relied for approval" (Fenofibrate Petition Response at 10, n. 14) (emphasis added), this was not the situation at issue in the Fenofibrate Petition. We subsequently have *required* an appropriate patent certification or statement to an "underlying NDA" only if the subsequent 505(b)(2) applicant specifically relied for approval on the drug product approved in the underlying NDA. . .

3. Pfizer's Reliance on Roxicodone and Revia in the Absence of a Pharmaceutical Equivalent

In addition to arguing that Pfizer must reference Reformulated OxyContin in its application for Troxyca ER, the Petition contends that Pfizer must reference the Agency's finding of safety and effectiveness for Targiniq ER because it is the drug "most similar" to Troxyca ER. Quoting language from the Fenofibrate Petition Response, the Petition argues that "'when a section 505(b)(2) [NDA] has been submitted and no pharmaceutically equivalent drug product has been previously approved, the 505(b)(2) applicant should choose the listed drug or drugs that are most similar to the drug for which approval is sought.'" Petition at 28-29, quoting the Fenofibrate Petition Response at 9-10.

The Petition acknowledges that in a 2013 citizen petition response,[34] FDA stated that the 2004 Fenofibrate Petition Response described a suggested approach that may enhance efficiency, but noted that listing the "most similar" drug is not required. Petition at 29. The Petition essentially asks that this policy be revisited to advance policy considerations, such as avoiding unnecessary research, allowing for efficient review by FDA, and to further the goals of the Hatch-Waxman Amendments. Id. at 30-34.

FDA Response

FDA has previously stated that if there is a listed drug that is a "pharmaceutical equivalent"[35] to the proposed drug product, the applicant should identify the pharmaceutically equivalent product as a listed drug relied upon and provide patent certifications for the patents listed for the pharmaceutically equivalent drug.[36] There is no listed drug that is a pharmaceutical equivalent to Troxyca ER, a fact that is not disputed in the Petition.

There is no statutory or regulatory requirement that an applicant rely upon the "most similar" product in its 505(b)(2) NDA as the Petition requests. Rather, "a sponsor interested in submitting a 505(b)(2) [NDA] that relies upon FDA's finding of safety and/or effectiveness for one or more listed drugs should determine which listed drug(s) is most appropriate for its development program."[37] Courts have recently upheld FDA's position on this issue.[38] If the applicant intends to submit a 505(b)(2) NDA that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, the applicant must establish that reliance on the

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[34] FDA Response to Hyman, Phelps, & McNamara, P.C. (September 18, 2013) (Docket Nos. FDA-2011-P-0869 and FDA-2013-P-0995) (Suboxone Petition Response).

[35] 21 CFR 320.1(c).

[36] Draft 505(b)(2) Guidance at 8; see also 80 FR 6802, 6855-56.

[37] Suboxone Petition Response at 7.

[38] Takeda Pharmaceuticals, U.S.A., Inc. v. Burwell, 2015 U.S. Dist. LEXIS 5908 (D.D.C. Jan. 13, 2015), *affirmed*, No. 15-5021 (D.C. Cir. July 15, 2016).

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