DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

MAR 21 2014

Peter R. Mathers
Jennifer A. Davidson
Kleinfeld, Kaplan and Becker, LLP
1140 Nineteenth Street, N.W.
Washington, DC 20036

Re: Docket No. FDA-2013-P-1375

Dear Mr. Mathers:

This letter responds to your citizen petition dated October 21, 2013 (the Petition). The Petition requests that the Food and Drug Administration (FDA or the Agency): (1) adopt and announce a guidance detailing certain specified *in vitro* and *in vivo* tests sufficient to establish that proposed generic products citing reformulated OxyContin (oxycodone hydrochloride (HCl) controlled-release) Tablets, new drug application (NDA) 22-272, as the reference listed drug (RLD) have equivalent abuse-deterrent (AD) properties as the RLD and can be expected to perform as well as the RLD when subjected to manipulations by individuals with the intent on abusing the product or by patients and/or caregivers inadvertently misusing the medication; (2) refuse to approve any abbreviated new drug application (ANDA) citing reformulated OxyContin as the RLD that does not include data from the proposed tests or includes data from such tests which fail to meet the proposed acceptance criteria; and (3) modify the draft bioequivalence guidance on oxycodone extended-release tablets to reflect the proposed testing requirements (Petition at 4-5).

We have carefully considered the Petition and comments submitted to the Docket. For the reasons stated below, the Petition is denied insofar as the Agency continues to consider the issues you raise, and granted insofar as the Agency intends to issue guidance regarding ANDAs and abuse-deterrent properties.[1]

[1] The Petition refers to three other citizen petitions filed by Purdue dated July, 13, 2012 (Docket No. FDA-2012-P-0760), August 28, 2012 (Docket No. 2012-P-0939), and February 22, 2013 (Docket No. FDA-2012-P-0939). The Petition states that all three citizen petitions remain pending (Petition 3).

The Petition states that the July 13, 2012 citizen petition was neither granted nor denied (Petition at 3). We note that Purdue's August 28, 2012, citizen petition states that it is "identical to that filed by [Purdue] on July 13, 2012 in Docket No. FDA-2012-P-0760, except for the date and certain, non-substantive changes to the 505(q) certification statement." Accordingly, FDA administratively closed Docket No. FDA-2012-P-0760. The memorandum requesting closure can be found at http://www.regulations.gov/#!documentDetail;D=FDA-2012-P-0760-0003.

CDER denied Purdue's August 28, 2012, citizen petition by letter dated January 23, 2013 (Docket No. FDA-2012-P-0939). Today, FDA also denied Purdue's February 22, 2013, citizen petition requesting reconsideration of CDER's January 23, 2013, decision (Docket No. FDA-2012-P-0939).

I. BACKGROUND

On December 12, 1995, FDA approved NDA 20-553 for OxyContin (oxycodone HCl controlled-release) Tablets. On April 5, 2010, FDA approved a second NDA (22-272) for a reformulated version of OxyContin (oxycodone HCl controlled-release) Tablets. Both products are opioid analgesics indicated for the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time.

Purdue Pharma (Purdue) is the holder of both NDAs. In correspondence dated August 10, 2010, Purdue notified FDA that it had ceased shipment of original OxyContin, and FDA thereafter moved original OxyContin to the "Discontinued Drug Product List" section of FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book).

In a letter dated March 19, 2013, Purdue requested that FDA withdraw approval of the original OxyContin NDA 20-553. In the Federal Register dated April 18, 2013, FDA published notice of its determination that original OxyContin was withdrawn for reasons of safety or effectiveness.[2] The notice concluded that "[o]riginal OxyContin . . . poses an increased potential for abuse by certain routes of administration, when compared to reformulated OxyContin. Based on the totality of the data and information available to the Agency at this time, FDA concludes that the benefits of original OxyContin no longer outweigh its risks."[3] The notice also stated that Agency will remove original OxyContin (NDA 20-553) from the Orange Book and FDA will not accept or approve ANDAs that reference it.[4] In the Federal Register dated August 7, 2013, FDA announced the withdrawal of approval of the original OxyContin (NDA 20-553), and noted that Purdue has voluntarily requested that approval of NDA 20-553 be withdrawn and has waived its opportunity for a hearing.[5]

II. DISCUSSION

A. Purdue's request that FDA issue guidance

Purdue requests that, for ANDAs citing OxyContin (NDA # 22-272) as the RLD, FDA:

> Adopt and announce a guidance detailing in vitro and in vivo tests sufficient to establish that proposed generic products have equivalent abuse-deterrent properties and can be expected to perform as well as

[2] "Determination That the OXYCONTIN (Oxycodone Hydrochloride) Drug Products Covered by New Drug Application 20–553 Were Withdrawn From Sale for Reasons of Safety or Effectiveness", 78 FR 23273.

[3] *Id.* at 23274.

[4] *Id.* at 23275.

[5] "Purdue Pharma L.P.; Withdrawal of Approval of a New Drug Application for Oxycontin"; 78 FR 48177.

reformulated OxyContin when subjected to manipulations by individuals intent on abusing the product or by patients/caregivers inadvertently misusing the medication, including at least the following:

(a) Tablet manipulation studies to determine the resistance of the proposed generic formulation to methods of reducing tablets to particles using a variety of commonly available tools, and to establish the time and effort required to reduce the proposed generic tablets to fine particles;

(b) In vitro small and large volume extraction and dissolution studies on intact tablets and on standardized particle sizes of manipulated tablets, using an appropriate range of solvents, conditions, and pretreatments;

(c) In vitro studies measuring the syringability and injectability of tablet contents, extracted by standardized procedures;

(d) In vitro studies measuring the ability to create and extract free oxycodone base from the tablets;

(e) In vitro smoking simulation studies measuring the ability to vaporize oxycodone from fine particles prepared from the tablets;

(f) An in vivo bioequivalence/non-inferiority study with clinical endpoints evaluating the abuse potential of orally ingested manipulated tablets (ingested after chewing, or after reducing the tablets to fine or coarse particles), providing measures of T_{max}, C_{max}, and AUC, and liking; and

(g) An in vivo bioequivalence/non-inferiority study with clinical endpoints evaluating the abuse potential of insufflated fine particles, providing measures (PK measures of T_{max}, C_{max}, and AUC, and liking); and

(h) Additional in vitro and/or in vivo tests necessary to evaluate any potential formulation-specific vulnerabilities associated with physical and chemical features of the generic product, using reformulated OxyContin as a control.

All of these tests should be comparative, using the reference listed drug OxyContin and powdered oxycodone API, as controls. The guidance should require, with respect to each in vitro and in vivo test, that generic products pass statistical analyses which demonstrate that they exhibit no greater rate or extent of oxycodone release or relative abuse potential than OxyContin.

As noted in the Petition (at pages 1-2), FDA has formed an internal working group and intends to issue guidance on the testing and evaluation of generic versions of opioid products with abuse-deterrent properties. At the September 30 – October 1, 2013, Abuse Deterrent Formulation Science Meeting held in Rockville, Maryland, Dr. Andre Raw of the Office of Generic Drugs discussed several of FDA's current internal and external initiatives on this topic.[6] The internal initiatives include testing of both approved products and internally-developed formulations to evaluate the robustness and reproducibility of in vitro tests and to develop optimal test conditions.[7] The external initiatives include the intended issuance of

[6] *Scientific Considerations for Abuse Deterrent Generic Opioid Drug Products*, Andre Raw, Director, Chemistry Division 1, Office of Generic Drugs, CDER (October 1, 2013), available at: http://nebula.wsimg.com/5dff082634bb819fcb1a145f9209903b?AccessKeyId=7B2DBB1E2E28C2F11192&disposition=0.

[7] Sarah Karlin, *Generics Of Abuse-Deterrent Opioids Will Get FDA Guidance, Eventually* - "*The Pink Sheet*," October 7, 2013, available at: http://www.elsevierbi.com/publications/the-pink-sheet/75/40/generics-of-abusedeterrent-opioids-will-get-fda-guidance-eventually.

guidance on which interested persons may comment, as well as a contract awarded in September 2013 for a study on evaluation of drug product formulation and in vitro performance characteristics related to abuse deterrence for solid oral dosage forms of opioids.[8] This study will investigate the effect of physicochemical properties of the active ingredient, excipients, and composition of the drug product, along with the drug product manufacturing technology, on the manipulation of the drug product for extraction of the active ingredient for abuse.[9] The external research study is intended to provide a better understanding of how material properties of formulation components impact abuse-deterrent properties.

These endeavors may provide useful information to help inform the Agency's thinking regarding abuse-deterrent properties.

B. Purdue's request regarding ANDAs

Purdue requests that FDA refuse to approve any ANDA citing OxyContin (NDA # 22-272) as the RLD that (a) does not include data from the in vitro and in vivo tests requested above, or (b) includes data from such tests which fail to meet the acceptance criteria requested above.

FDA only intends to approve ANDAs that meet the statutory and regulatory requirements for approval (see generally section 505(j) of the FD&C Act (21 U.S.C. 355(j)) and 21 CFR 314.94, 314.105 & 314.127). As with any ANDA approval decision, FDA's decision to approve any particular ANDA referencing reformulated OxyContin will be based on the adequacy of data and information supporting the ANDA.

C. Purdue's request regarding the draft bioequivalence guidance on oxycodone extended release tablets

Purdue requests that FDA modify the draft bioequivalence guidance on oxycodone extended release tablets to reflect the test requirements above. FDA issued the draft bioequivalence guidance for oxycodone extended-release tablets in July 2010.[10] As with any Agency guidance development process, we intend to consider relevant scientific information and revise, re-issue, or finalize the bioequivalence guidance for oxycodone extended-release tablets, as appropriate.

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[8] The contract was awarded to the National Institute for Pharmaceutical Technology and Education, a consortium of 13 universities with expertise in pharmaceutical science, for a 2-year period to conduct research into in vitro testing of abuse-deterrent formulations. Notice of award available at: https://www.fbo.gov/index?mode=form&id=e679fb037d222e610542317012e0f495&tab=ntype; *See also* request for information available at: https://www.fbo.gov/index?s=opportunity&mode=form&id=81097151079184467f03b5fcb431b4f2&tab=core&_cview=0.

[9] *Id.*

[10] This draft guidance is available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM220198.pdf.

III. CONCLUSION

For the reasons described above, the Petition is denied insofar as the Agency continues to consider the issues you raise, and granted insofar as the Agency intends to issue guidance regarding ANDAs and abuse-deterrent properties.

Sincerely,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research