DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

MAY 10 2013

Robert Barto
Vice President, Regulatory Affairs
Endo Pharmaceuticals Inc.
1400 Atwater Drive
Malvern, PA 19355

Re: Docket No. FDA-2012-P-0895

Dear Mr. Barto:

This letter responds to a citizen petition (the Petition) you submitted on behalf of Endo Pharmaceuticals Inc. (Endo). The Petition, received on August 13, 2012, requests that the Food and Drug Administration (FDA): (1) determine that Opana ER (oxymorphone hydrochloride) Extended-Release Tablets approved under new drug application (NDA) 21-610 were discontinued for reasons of safety, (2) refuse to approve any pending abbreviated new drug application (ANDA) for a generic version of Opana ER approved under NDA 21-610, and (3) suspend and withdraw the approval of any ANDA referencing Opana ER approved under NDA 21-610 as the reference listed drug (RLD) (Petition at 1).

We have carefully considered the Petition, supplements, and comments to the Petition docket. For the reasons summarized below, the Petition is denied.[1] FDA has determined that Opana ER approved under NDA 21-610 was not withdrawn from sale for reasons of safety or effectiveness. Accordingly, this product will remain listed in the "Discontinued Drug Product List" section of *Approved Drug Products With Therapeutic Equivalence Evaluations* (the Orange Book).[2] As a result, ANDAs referencing NDA 21-610 may be approved as long as they meet all other legal and regulatory requirements for the approval of ANDAs, and we will not begin procedures to suspend or withdraw approval of ANDAs that reference NDA 21-610.

[1] Endo's submissions contain attachments marked "confidential." Endo also states in a supplement to its Petition (April 23, 2013, p.6) that it submitted in support of NDA 201-655 (the reformulated Opana ER NDA) studies demonstrating that reformulated Opana ER is resistant to crushing, and notes these studies are described in another citizen petition submitted by Endo on August 31, 2012 (Docket No. FDA-2012-P-0951). Because of potential disclosure implications, this response discusses these data and our assessment of the data only in general terms.

[2] The "Discontinued Drug Product List" includes products that have been discontinued from marketing for reasons other than safety or effectiveness.

# I. BACKGROUND

## A. Original and Reformulated Opana ER

Opana ER (oxymorphone hydrochloride) Extended-Release Tablets (OP) are the subject of NDA 21-610, held by Endo and initially approved by FDA on June 22, 2006. The approved labeling stated that the product should be swallowed whole, and warned that crushing, chewing, snorting, or injecting the dissolved product will result in uncontrolled delivery and pose significant risk that could result in overdose and death.

In December 2010, FDA approved two ANDAs that reference OP. One entered the market in July 2011;[3] the other entered the market in January 2013.[4]

A reformulated version of OP, also called Opana ER (oxymorphone hydrochloride) Extended-Release Tablets (OPR), is the subject of NDA 201-655, also held by Endo and initially approved by FDA on December 9, 2011. Endo's original NDA for OPR included data from studies designed to assess the potentially abuse-deterrent properties of the new formulation. Although FDA approved the application in December 2011 because it concluded that OPR was safe and effective, the approved labeling did not describe any abuse-deterrent properties.[5] To date, the "abuse potential" subsection of the "Warnings and Precautions" section and "Drug Abuse and Dependence" section of the OPR and OP product labeling are virtually identical.[6]

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[3] See *Actavis U.S. Launches Oxymorphone Hydrochloride Extended-Release Tablets, CII*, available at http://www.actavis.com/en/media+center/PressReleases/articles/oxymorphone_hcl_extended_release_us.htm.

[4] See *Press Release: Impax Laboratories Launches Oxymorphone Hydrochloride Extended-Release Tablets*, available at http://investors.impaxlabs.com/Media-Center/Press-Releases/Press-Release-Details/2013/Impax-Laboratories-Launches-Oxymorphone-Hydrochloride-Extended-Release-Tablets1132511/default.aspx.

[5] See Summary Review for Regulatory Action NDA 21-655(January 7, 2011) at (http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/201655Orig1s000MedR.pdf); Summary Review for Regulatory Action NDA 201-655 (Dec. 9, 2011) at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/201655Orig1s000SumR.pdf ("While the new formulation has demonstrated a minimal improvement in resistance to tampering by crushing, thereby limiting the likelihood of abuse by crushing followed by ingestion, and by insufflation (snorting) to some degree, it can still be. . . cut . . . rendering it readily abusable by ingestion and intravenous injection, and possibly still by insufflation; although whether . . . tablets can be snorted was not studied. Of more concern, when chewed . . . the new formulation essentially dose dumps like an immediate-release formulation ."); Cross-Discipline Team Leader Review for NDA 201-655 (second review cycle) (November 30, 2011) at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/201655Orig1s000CrossR.pdf; See also product labeling for NDA 201-655 (December 9, 2011) at http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/201655lbl.pdf.

[6] Compare most current product labeling for OP (NDA 21-610/S-13; July 9, 2012) (http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021610s013lbl.pdf) and most current product labeling for OPR (NDA 201-655/S-04; January 14, 2013) (http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/201655s004lbl.pdf).

### B. Relisting Petition and Lawsuit

Endo withdrew the 7.5 mg and 15 mg strengths of OP from sale in March 2011.[7] On May 31, 2012, Endo notified FDA that it had ceased shipping all strengths of OP. In August 2012, Endo submitted the Petition, which asks FDA to determine that OP was withdrawn for safety reasons (Petition at 1, 6, 10).

Endo sued FDA on November 30, 2012, alleging that FDA had improperly failed to decide in a timely manner whether OP was withdrawn from sale for safety or effectiveness reasons and asking the court to order FDA to make this determination by December 31, 2012.[8] FDA asked the court to dismiss Endo's complaint, noting that under the relevant section of the Federal Food, Drug, and Cosmetic Act (the FD&C Act), the agency was not required to determine whether Endo had withdrawn OP from sale for safety or effectiveness reasons until May 10, 2013.[9] The Court dismissed Endo's complaint on December 19, 2012.

Endo supplemented its Petition on November 13, 2012 and March 21, 2013 with preliminary postmarketing data and analysis concerning abuse of OP, generic versions of OP, and OPR. Endo further supplemented its Petition on April 23, 2013.

### C. Summary of Legal Framework

In the 1980's, Congress enacted the Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417) (the 1984 amendments), which authorized the approval of duplicate versions of drug products (commonly referred to as "generic drugs") under an abbreviated procedure. ANDA applicants must show that the drug for which they are seeking approval has the same active ingredient, route of administration, dosage form, strength and, with certain exceptions, labeling as and is bioequivalent to the "listed drug," which is a version of the drug that was previously approved. ANDA applicants do not have to repeat the extensive clinical testing otherwise necessary to gain approval of a new drug application (NDA) (505(j) of the FD&C Act).

Under section 505(j)(7) of the FD&C Act (21 U.S.C. 355(j)(7)), FDA is required to publish a list of all approved drugs. FDA publishes this list as part of the *Approved Drug Products With Therapeutic Equivalence Evaluations*, which is known generally as the *Orange Book.*

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[7] FDA determined that Opana ER (oxymorphone HCl) extended-release tablets, 7.5 mg and 15 mg, were not withdrawn from sale for reasons of safety or effectiveness. See 76 Fed. Reg. 53,908 (August 30, 2011).

[8] See Complaint for Mandatory, Declaratory, and Injunctive Relief, *Endo Pharmaceuticals Inc. v. FDA et al*, Civil Action 12-1936 (D.D.C. 2012).

[9] See Consolidated Memorandum in Support of Federal Defendants' Motion to Dismiss and in Opposition to Plaintiff's Motion for a Preliminary Injunction, *Endo Pharmaceuticals Inc. v. FDA et al*, Civil Action 12-1936 (D.D.C. 2012).

Drugs are removed from the list if the Agency determines that the listed drug was withdrawn from sale for reasons of safety or effectiveness (505(j)(7)(C) of the FD&C Act; 21 CFR 314.162). In addition, if the listed drug has been withdrawn from sale for safety or effectiveness reasons, the approved ANDAs that refer to the listed drug must be withdrawn or suspended (505(j)(6)(C) of the FD&C Act).

A person may petition the Agency to determine (or the Agency may determine on its own initiative) whether a listed drug was withdrawn from sale for reasons of safety or effectiveness (21 CFR 314.161). Under section 505(w) of the FD&C Act, FDA must issue a final, substantive determination on such a petition "no later than 270 days after the date the petition is submitted" (21 U.S.C. 355(w)).[10] Further, FDA must determine whether a listed drug was withdrawn from sale for reasons of safety or effectiveness before approving any ANDAs that refer to the listed drug or if any approved ANDAs refer to the listed drug (21 CFR 314.161(a)).

The NDA holder's stated reasons for withdrawing the drug are not determinative. 57 Fed. Reg. at 17971 (Apr. 28, 1992). The agency "will...consider other factors...such as increases in the number of adverse drug reactions reported on the drug and published or unpublished studies of the drug questioning its safety or effectiveness." 54 Fed. Reg. at 28907 (July 10, 1989).

FDA has long considered the abuse potential of a drug in numerous regulatory contexts. Where appropriate, FDA may take abuse potential into account when weighing a drug's benefits and risks. The agency has also recognized that a drug's benefit/risk profile can change due to the availability of alternative products.[11] Recently, the agency considered the increased potential for abuse of original OxyContin (oxycodone hydrochloride) Extended-Release Tablets relative to reformulated OxyContin (oxycodone hydrochloride) Extended-Release Tablets in determining that original OxyContin was withdrawn for safety or effectiveness reasons.[12]

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[10] This provision was added by section 1134(a) of the Food and Drug Administration Safety and Innovation Act (Public Law 112-144, 126 Stat. 1075).

[11] For example, FDA determined that the 10 mg presentation of Halflytely and Bisocodyl Tablets Bowel Prep Kit was withdrawn for safety reasons because the 5 mg presentation had "comparable effectiveness to the 10 mg product and...a safety advantage over the 10 mg product[.]" 76 Fed. Reg. 51037 (Aug. 17, 2011).

[12] 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 Fed. Reg. 23,273 (April 18, 2013).

## II. DISCUSSION

### A. The Available Data Do Not Support Endo's Conclusions Regarding Purported Safety Advantages of OPR Relative to OP.

Endo contends that OPR offers "safety advantages" over OP because OPR "is resistant to crushing by common methods and tools employed by abusers of prescription opioids ... [and] is less likely to be chewed or crushed even in situations where there is no intent for abuse, such as where patients inadvertently chew the tablets, or where caregivers attempt to crush the tablets for easier administration with food or by gastric tubes, or where children accidentally gain access to the tablets" (Petition at 8). In its April 2013 supplement, Endo states that it submitted in support of NDA 201-655 in vitro manipulation and extraction studies, pharmacokinetic studies, and clinical studies demonstrating that OPR is resistant to crushing compared to OP for purposes of intranasal or injectable use. Endo notes that these studies are described in a separate citizen petition Endo submitted on August 31, 2012, and can be found in NDA 201-655 (Docket No. FDA-2012-P-0951). Endo contends that preliminary postmarketing data show a significant reduction in overall and non-oral OPR abuse rates compared to baseline OP abuse rates, as well as a significant increase in the overall and non-oral abuse rates of generic versions of OP following the replacement of OP with OPR in the market.[13]

We disagree with Endo's conclusions about OPR's alleged safety advantages. While there is an increased ability of OPR to resist crushing relative to OP, data from in vitro and pharmacokinetic studies show that OPR's extended-release features can be compromised, causing the product to "dose dump," when subjected to other forms of manipulation such as cutting, grinding, or chewing, followed by swallowing.[14,15] It also

[13] See November 13, 2012, Supplement to Petition at 2-7; March 21, 2013, Supplement to Petition at 3, 6-12.

[14] Although it is possible that OPR's crush-resistance may deter some misuse, such as improper crushing for administration with food or through a feeding tube, OPR appears to remain susceptible to other types of therapeutic or unintentional misuse, such as causing the product to "dose dump" by cutting or chewing and then swallowing. Inclusion of language regarding reduced crushability in the labeling could be misleading and result in health care practitioners or patients thinking that OPR is safer than OP, and that it is safe to chew OPR; or that it is safe to give OPR to vulnerable populations (e.g., cognitively impaired) who may chew the product if not adequately supervised. See Summary Review for Regulatory Action (January 7, 2011) at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/201655Orig1s000MedR.pdf.

[15] Although Endo states that it submitted bioavailability data demonstrating that attempted crushing of OPR with a commercial pill crusher had no effect on relative bioavailability and extended-release profile of OPR (April 2013 supplement cross-referencing August 31, 2012 Petition pp. 8-9), other data, as noted in the text, show that other forms of manipulation can compromise OPR's extended release features causing it to dose dump. See e.g., Summary Review for Regulatory Action (January 7, 2011) at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/201655Orig1s000MedR.pdf; Summary Review for Regulatory Action (December 9, 2011) at http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/201655lbl.pdf. Endo's Petition and supplements make other assertions regarding crushing, but do not address chewing, cutting, and grinding.

appears that OPR can be prepared for insufflation (snorting) using commonly available tools and methods.[16] OPR can be readily prepared for injection, despite Endo's claim that OPR tablets have "resistance to aqueous extraction (i.e., poor syringeability)" (Petition at 4).[17] In addition, certain data suggest that OPR can more easily be prepared for injection than OP.[18]

Moreover, the data from the postmarketing investigations Endo relies on are inconclusive and, as the company repeatedly acknowledges, "preliminary."[19] They include only 2 to 3 quarter-years of data following introduction of OPR, and suffer from significant additional deficiencies (including small sample sizes, likely misclassification of drug exposure, and possibly artificially elevated OP baseline abuse rates[20]), such that it is not possible to draw meaningful conclusions based on them.[21]

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[16] In particular, as noted in the Summary Review for Regulatory Action (January 7, 2011) and a Discipline Review Letter (January 4, 2011), OPR can be ground for possible insufflation. Accordingly, FDA recommended that a study be conducted to determine whether ground OPR could be administered intranasally, if such a study could be conducted safely. See (http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/201655Orig1s000MedR.pdf); see also (http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/201655Orig1s000AdminCorres.pdf. Endo's Petition and supplements do not discuss such a study and only refer to manipulation using simple tools such as a hammer, pill crusher, and two spoons, which are not sufficient to fully assess whether OPR is suitable for insufflation or to assess clinical preference for insufflation by experienced drug users. Endo states (April 2013 Supplement cross-referencing August 31, 2012 Petition, pp. 7-8) that (1) users in a particular study were largely unwilling to snort the resulting broken materials made from OPR; and (2) that approximately 96% of subjects were willing to snort tampered OP compared with 11% of subjects for OPR. But subjects in that study largely attempted to tamper with OPR using tools and methods other than grinding. See Vosburg et al, Assessment of a formulation designed to be crush-resistant in prescription opioid abusers. 126 Drug Alcohol Depend. pp. 206-15 (2012), available at http://dx.doi.org/10.1016/j.drugalcdep.2012.05.013. Accordingly, this study does not provide adequate data with which to assess possible intranasal abuse of ground OPR.

[17] Endo also claims that OPR "gradually forms a viscous hydrogel" when "subjected to an aqueous environment" (April 23 Supplement to Petition at 3).

[18] See e.g., Summary Review for Regulatory Action (January 7, 2011) at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/201655Orig1s000MedR.pdf.

[19] See, e.g., March 21, 2013 Supplement to Petition at 2, 4, 6.

[20] The investigations Endo relies upon use OP abuse rates from 2011 as the baseline comparator against which OPR abuse rates are measured. Endo states that 2011 saw an increase in OP abuse from 2010, and it states that this increase may be caused by the launch of reformulated OxyContin (which was designed to be difficult to manipulate for purposes of abuse and was determined by FDA to have certain abuse-deterrent properties). It is too early to say whether the 2011 OP abuse rates represent the appropriate baseline risk or an aberration.

[21] If one were to treat the available data as a reliable indicator of abuse rates despite the data limitations noted above, one of the postmarketing investigations suggests the troubling possibility that a higher (and rising) percentage of OPR abuse is occurring via injection than was the case with OP. Abuse via injection is highly dangerous, and injection of OPR in particular has been associated with a serious thrombotic thrombocytopenic purpura (TTP)-like illness. See "FDA warns about serious blood disorder resulting from misuse of Opana ER," dated October 11, 2012, and updated on November 1, 2012, available at http://www.fda.gov/Drugs/DrugSafety/ucm322432.htm; Centers for Disease Control and Prevention, Morbidity and Mortality Weekly Report, Vol. 62, No. 1, January 11, 2013. TTP is a serious blood disorder

While FDA considers the development of abuse-deterrent formulations a high public health priority, such properties must be supported by adequate data.

### B. Endo's Assertion that OPR and Reformulated OxyContin have "Virtually Identical" Abuse-Deterrent Properties is Misplaced and Without Merit.

In its April 2013 supplement, Endo contends that FDA should make the same determination regarding OP as it did regarding original OxyContin (OC) because OPR and reformulated OxyContin (OCR) "have virtually identical abuse-deterrent properties…[as] demonstrated through the data Endo submitted in support of NDA No. 201655, post-marketing epidemiology data, and the similar physicochemical properties between both [OPR] and [OCR]."[22]

We disagree. The abuse-deterrent properties of OPR and OCR and the resulting regulatory implications have been the subject of independent, extensive consideration by Agency experts over the course of many months.[23] Our decisions take into account the totality of the evidence for the particular drug at issue, and must be made on a case-by-case basis. Accordingly, any attempt by Endo to draw parallels between OCR and OPR and thereby make assumptions regarding the regulatory implications for OP is misplaced.

Nonetheless, we note that there are differences in the products and the available data such that it is reasonable to draw different conclusions. Based on in vitro, pharmacokinetic, clinical abuse potential, and post-marketing data, we were able to conclude that OC posed an increased potential for intranasal abuse compared to OCR. In vitro data showed that OCR required more effort, time, experience, and tools to create a fine powder for intranasal abuse than OC. A clinical abuse potential study showed that most study subjects liked finely ground OCR less than finely ground OC following attempted snorting. Pharmacokinetic and post-marketing data were also supportive of our conclusions regarding intranasal abuse of OCR.

While the available data show that there is an increased ability of OPR to resist crushing relative to OP, OPR still can be prepared for insufflation (snorting) using commonly available tools and methods. Endo's Petition and supplements do not describe a clinical abuse potential study to assess the ability to insufflate or clinical preferences.[24] Further,

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characterized by microangiopathic hemolytic anemia and thrombocytopenia. FDA's review has not revealed this association with any other opioid analgesic.

[22] April 23 Supplement to the Petition at 6.

[23] For OxyContin, see Dr. Throckmorton Memo re: Purdue's reformulated OxyContin (oxycodone hydrochloride) extended release tablets (April 16, 2013) at (http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/022272Orig1s014_ODMemo.pdf; 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 Fed. Reg. 23,273 (April 18, 2013).

[24] See footnote 16.

the preliminary data from the Opana ER post-marketing investigations have significant limitations and are not as mature as the OxyContin postmarketing investigations, which themselves were only supportive, and not conclusive, of reduced intranasal abuse.

Based on in vitro and post-marketing data, we were able to conclude that OC posed an increased potential for abuse via injection compared to OCR. The in vitro data showed that OCR has physicochemical properties expected to make abuse by injection difficult. When subjected to an aqueous environment, OCR gradually forms a viscous hydrogel that resists passage through a needle such that it prevents oxycodone from being drawn into a syringe to any meaningful extent. Postmarketing data were supportive of our conclusions regarding abuse of OCR via injection. In contrast, OPR can be readily prepared for injection and preliminary data from the Opana ER post-marketing investigations have significant limitations, as discussed above.[25]

In sum, while there were sufficient data to conclude that OC posed an increased potential for abuse by certain routes of administration compared to OCR, there currently are *not* sufficient data to conclude that OP poses an increased potential for abuse compared to OPR.

### C. OP Was Not Withdrawn for Safety or Effectiveness Reasons.

We have conducted an extensive review of the issues raised by Endo and have concluded that while OPR and OP have the same therapeutic benefits, there is insufficient evidence that OP has an increased potential for abuse compared to OPR. Based on the totality of the data and information available to the Agency, FDA has determined that OP's benefits continue to outweigh its risks. Therefore, OP was not withdrawn from sale for reasons of safety or effectiveness.

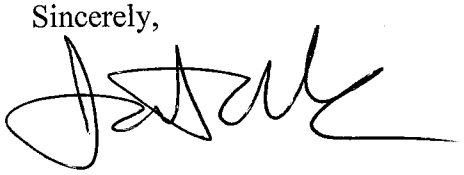
The Agency will continue to list OPANA ER (oxymorphone HCl) extended-release tablets approved under NDA 21-610 in the "Discontinued Drug Product List" section of the Orange Book. FDA will not begin procedures to withdraw approval of ANDAs that refer to these drug products. Additional ANDAs that refer to Opana ER (oxymorphone HCl) extended-release tablets may be approved by the Agency as long as they meet all other legal and regulatory requirements for the approval of ANDAs. FDA plans to publish a notice announcing this determination in the *Federal Register*.

[25] If one were to treat the available post-marketing data from the Opana ER investigations as a reliable indicator of abuse rates despite these limitations, these data appear to suggest that a greater (and rising) percentage of Opana ER abusers are abusing Opana ER via injection since the replacement of OP with OPR in the market. This suggestion would be consistent with in vitro data showing that while it may be more difficult to prepare OPR for insufflation using certain tools (although it is possible to do so using other tools) it may actually be *easier* to prepare OPR for injection. Taken together, these data suggest the troubling possibility that the reformulation may be shifting a non-trivial amount of Opana ER abuse from snorting to even more dangerous abuse by intravenous or subcutaneous injection.

## III. CONCLUSION

For the reasons explained above, the Petition is denied.

Sincerely,



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