FDA U.S. FOOD & DRUG ADMINISTRATION

NOV 2 8 2016

Kurt R. Karst
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700 Thirteenth Street NW Suite 1200
Washington, DC 20005-5929

Re: Docket No. FDA-2016-P-1946

Dear Mr. Karst:

This letter responds to your citizen petition dated July 1, 2016 (Petition), submitted on behalf of Collegium Pharmaceutical, Inc. (Collegium). Your Petition requests that the Food and Drug Administration (FDA or Agency) refuse to approve any pending new drug application (NDA) or supplemental NDA for an oxycodone extended-release drug product unless such drug product includes abuse-deterrence labeling, based on premarket studies conducted in Categories 1, 2, and 3 as identified in FDA's guidance for industry, *Abuse-Deterrent Opioids – Evaluation and Labeling* (April 2015) (the Evaluation and Labeling Guidance),[1] that show abuse-deterrence that is equivalent or superior to Xtampza ER (oxycodone) extended-release capsules (NDA 208090). (Petition at 3.) That is, these data must show, according to your Petition, that "the [oxycodone ER] drug product is not less abuse-deterrent, and therefore, not less safe, than Xtampza ER" (Petition at 26).

We have carefully reviewed your Petition, all comments submitted on the Petition, and other information available to the Agency. For the reasons stated below, your Petition is denied insofar as the agency continues to consider the complex scientific issues you raise and is unable to resolve them within the 150-day timeframe set forth in section 505(q) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(q)).

I. BACKGROUND

A. Xtampza ER

In April 2016 the Agency approved NDA 208090 for Collegium's Xtampza ER (oxycodone) extended-release capsules (9 milligram (mg), 13.5 mg, 18 mg, 27 mg, and 36 mg strength) to treat pain severe enough to require daily, around-the-clock, long-term opioid treatment for which alternative treatment options are inadequate. Xtampza ER is approved with labeling describing the product's abuse-deterrent properties consistent with the Evaluation and Labeling Guidance. Specifically, the approved labeling states in relevant part that:

> The in vitro data demonstrate that Xtampza ER has physicochemical properties expected to make abuse by injection difficult. The data from pharmacokinetic and human abuse potential studies, along with support from in vitro data, also indicate that Xtampza ER has physicochemical properties that are expected to reduce abuse via the intranasal route.[2]

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[1] Available at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm334743.pdf. We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[2] See Section 9.2 (Abuse) of the FDA-approved labeling for Xtampza ER (NDA 208090) at http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/208090s000lbl.pdf.

B. Section 505(q) of the FD&C Act

Section 505(q) of the FD&C Act was added by section 914 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Pub. L. 110-85, 121 Stat. 823) and was amended by the Food and Drug Administration Safety and Innovation Act (FDASIA) (Pub. L. 112-144, 126 Stat.993). Section 505(q) of the FD&C Act applies to certain citizen petitions and petitions for stay of Agency action that request FDA take any form of action relating to a pending application submitted under section 505(b)(2) or (j) of the FD&C Act. Section 505(q) also governs the manner in which these petitions are treated. Among other things, section 505(q)(1)(F) governs the time frame for final Agency action on a petition subject to section 505(q). Under this provision, FDA must take final Agency action on a petition no later than 150 days after the date on which the petition is submitted. The 150-day period is not to be extended for any reason.

II. DISCUSSION

Your Petition raises complex scientific and policy issues that FDA cannot resolve within the 150-day time frame set forth in section 505(q) of the FD&C Act. Accordingly, as explained below, we deny your petition without comment on the specific requirements for approval of an NDA or supplemental NDA for an oxycodone extended-release drug product.

A. FDA Supports the Development of Abuse-Deterrent Opioids

FDA considers the transition of the prescription opioid market from conventional to abuse-deterrent products a public health priority, and supports that priority in several ways:

- FDA has consulted with advisory committees on many occasions in connection with the development, evaluation, and labeling of abuse-deterrent opioids.
- In the fall of 2014, FDA hosted a public meeting regarding the development and regulation of abuse-deterrent opioids.[3]
- In April 2015, FDA published the final version of the Evaluation and Labeling Guidance, and has approved labeling describing the expected abuse-deterrent properties of seven extended-release solid oral dosage form opioid drug products to date (including Xtampza ER).[4]
- In February 2016, FDA issued an Opioids Action Plan which, among other actions intended to combat the opioid abuse epidemic, notes FDA's continued support for the development of more effective abuse-deterrent features.[5]
- In March 2016, FDA published a draft guidance on the evaluation and testing of generic versions of solid oral dosage form abuse-deterrent opioids,[6] and hosted a public meeting on October 31 and November 1, 2016 to obtain feedback on this guidance (as well as other issues regarding the

[3] See "Development and Regulation of Abuse-Deterrent Formulations of Opioid Medications; Public Meeting," 79 FR 56810 (September 23, 2014), Docket No. FDA-2014-N-1359. See also FDA's Web page describing this meeting and posting selected meeting materials, available at http://www.fda.gov/Drugs/NewsEvents/ucm408607.htm.

[4] See FDA Fact Sheet — FDA Facts: Abuse-Deterrent Opioid Medications, available at http://www.fda.gov/NewsEvents/Newsroom/FactSheets/ucm514939.htm.

[5] See Fact Sheet – FDA Opioids Action Plan, available at http://www.fda.gov/NewsEvents/Newsroom/FactSheets/ucm484714.htm.

[6] See draft guidance for industry, *General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products* (March 2016), available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM492172.pdf. When final, this guidance will represent the FDA's current thinking on this topic.

premarket evaluation of abuse-deterrent opioids).[7] The agency expects that the availability of less costly generic versions of abuse-deterrent opioids should accelerate prescribers' uptake of abuse-deterrent opioids.

As you know, FDA has required sponsors of products with approved labeling describing their abuse-deterrent properties, including Xtampza, to conduct studies to assess the impact of those properties on abuse in the real world setting.[8]

B. FDA Makes Product-by-Product Decisions Regarding the Regulation of Opioids

The science of abuse deterrence is relatively new, and both the formulation technologies and the analytical, clinical, and statistical methods for evaluating those technologies are rapidly evolving. FDA strongly supports a transition to abuse-deterrent opioids, but at this time only a few such products are on the market. The vast majority of opioid products dispensed are conventional (i.e., non-abuse-deterrent) products, most of which are generic drug products. There are, as yet, no approved generic versions of any of the abuse-deterrent opioid drug products.

Furthermore, the labeling of all approved abuse-deterrent opioid products approved to date indicates only that these products are *expected* to deter abuse by various routes (e.g., intranasal, injection) -- we do not yet have sufficient data to confirm these expectations for any of these products. In addition, the labeling of each abuse-deterrent opioid states that additional data may provide further information on the impact of the product's abuse-deterrent properties on the abuse liability of the drug, and that the labeling describing the product's expected abuse-deterrent properties may be updated as appropriate.[9] While FDA has required the sponsors of these products to conduct postmarket studies intended to help FDA determine whether and to what extent these products actually deter abuse, these studies are ongoing and not expected to be completed for some time. For example, the formal observational studies of Xtampza's abuse-deterrent properties are slated for completion by December 2020, with a final report to be submitted to FDA by June 2021.[10]

Under FDA's current approach, abuse potential, including the presence and effectiveness of any abuse-deterrent properties, is one aspect of a product's safety that FDA considers, together with all other appropriate factors, in determining whether an opioid drug product's benefits outweigh its risks. FDA takes into consideration available alternative therapies as part of this risk-benefit assessment. In light of the need for further data and scientific development in this nascent and rapidly evolving area, however, FDA intends to continue to take a product-by-product approach to regulatory decisions concerning the safety and effectiveness of opioid products, including extended-release oxycodone products. Accordingly, FDA cannot resolve the issues raised by your Petition within the 150-day time frame imposed by section 505(q) of the FD&C Act, and will deny your Petition without comment on the specific requirements for approval of an NDA or supplemental NDA for an extended-release oxycodone product. FDA will continue to consider the issues raised by your petition, as appropriate, when evaluating NDAs and supplemental NDAs for extended-release oxycodone products. As the science of abuse-deterrent technologies continues to develop, we will continue to evaluate our approach to regulatory decisions concerning these products.

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[7] See Public Meeting on Pre-Market Evaluation of Abuse-Deterrent Properties of Opioid Drug Products, 81 FR 69532 (October 6, 2016), Docket No. FDA-2016-N-2896.

[8] See FDA Facts: Abuse-Deterrent Opioid Medications, available at http://www.fda.gov/NewsEvents/Newsroom/FactSheets/ucm514939.htm; see also approval letters for Embeda, Hysingla ER, MorphaBond, OxyContin, Targiniq ER, Troxyca ER, and Xtampza ER.

[9] See, e.g., Section 9.2 (Abuse) of the labeling of Xtampza ER (NDA 208090), available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/208090s000lbl.pdf.

[10] Xtampza ER Approval Letter (April 26, 2016) at 8-9.

III. CONCLUSION

For the reasons described in this response, the Petition is denied.

Sincerely,

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