MEMORANDUM

TO: New Drug Application File for TROXYCA ER (oxycodone hydrochloride and naltrexone hydrochloride) Extended Release Capsules (NDA 207621)

CC: Office of Regulatory Policy Citizen Petition File (FDA-2016-P-1946), Carol Bennett, Deborah Livornese (ORP), Curt Rosebraugh (ODE I), Ellen Fields (DAAAP), Gerald Dal Pan, Judy Staffa, Cynthia Kornegay (OSE), Doug Throckmorton (CDER)

FROM: Patrick Raulerson (Senior Regulatory Counsel, DRP IV, ORP)
Sharon Hertz, MD (Division Director, DAAAP)

DATE: August 19, 2016

SUBJECT: Citizen Petition from Collegium Pharmaceutical, Inc. re: oxycodone extended-release products (FDA-2016-1946)

This memorandum summarizes the agency's current thinking regarding the issues raised in the pending citizen petition submitted under section 505(q) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) by Collegium Pharmaceutical, Inc. (the Collegium petition) as they relate to FDA's approval of TROXYCA® ER (oxycodone hydrochloride and naltrexone hydrochloride) extended-release capsules (Troxyca ER).

As explained in section III of this memorandum, FDA has determined that Troxyca ER is safe and effective and can be approved under section 505 of the FD&C Act. We have also determined that the issues raised in the Collegium petition do not preclude approval or otherwise alter that determination with respect to Troxyca ER.

FDA is still otherwise considering the issues raised in the Collegium petition, and intends to respond on or before the statutory deadline associated with the petition, November 28, 2016.

I. Collegium Petition

The Collegium petition requests that FDA refuse to approve any pending new drug application (NDA) or supplemental NDA for an oxycodone extended-release (ER) drug product unless: (1) such drug product bears 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),[1] (the Evaluation and Labeling Guidance); and (2) those studies show that the product's abuse-deterrent properties are "equivalent or superior to" Xtampza ER (oxycodone) extended-release capsules (NDA 208090). (Collegium petition at 3.)

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[1] Available at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm334743.pdf.

characterization of what the data mean, is included in the labeling for Troxyca ER (*See* Evaluation and Labeling Guidance standard at 22.)

FDA's rationale for approving Troxyca ER for the above-stated indication and with labeling describing the product's abuse-deterrent properties is set forth in the appropriate review documents, including Dr. Sharon Hertz's August 19, 2016, Summary Review for Regulatory Action. This memorandum focuses on FDA's determination that the issues raised in the Collegium petition do not preclude approval of or otherwise alter the agency's decision to approve Troxyca ER.

III. Discussion

FDA is approving Troxyca ER with labeling describing its abuse-deterrent properties based on the full range of premarket studies, including Category 1 (in vitro), Category 2 (pharmacokinetic), and Category 3 (clinical abuse potential) studies, described the Evaluation and Labeling Guidance. As such, Troxyca ER's labeling is expected to include "abuse-deterrence labeling, based on premarket studies conducted in Categories 1, 2, and 3 identified in the [Evaluation and Labeling Guidance]." (Collegium petition at 3.)

FDA has concluded that both Xtampza ER and Troxyca ER can be expected to meaningfully deter abuse, and thus has approved (or, in the case of Troxyca ER, is approving) labeling for each describing the product's abuse-deterrent properties. However, at this time, the available pre-market data are not yet sufficient to assess the capacity of Troxyca to deter abuse relative to Xtampza ER in real world settings. We summarize below considerations and complexities involved in making such a determination.

A. Postmarketing data are generally needed to assess the impact of abuse-deterrent properties in the community

First, premarket data on abuse-deterrent properties generally allow FDA to determine that a product can be *expected* to deter abuse by one or more routes, but FDA requires that sponsors of all such products conduct postmarket studies to assess the actual impact of their products' abuse-deterrent properties on the prevalence and consequences of abuse. Accordingly, when labeling describing abuse-deterrent properties is based on premarket studies, it states only that the properties are "expected" to have an impact on abuse, and further explains that the labeling may be revised based on postmarketing experience. FDA explained the relationship between premarket and postmarket studies in the Evaluation and Labeling Guidance as follows:

> [P]remarket studies are intended to demonstrate properties that are predictive of a meaningful abuse-deterrent effect for a particular route of administration. FDA has limited data correlating the abuse-deterrent properties of certain opioid drug products, as demonstrated by premarket studies, with the impact of those properties on abuse or adverse events associated with abuse in the post-approval setting. Even though postmarket studies have the potential to demonstrate such effects, the findings of postmarket studies are not available at the time of initial product approval. Labeling

B. FDA intends to continue to make regulatory decisions regarding Troxyca ER and other opioids on a case-by-case basis with appropriate consideration of available therapies and in a manner that is consistent with how we regulate drugs in other therapeutic areas

FDA intends to continue to assess the benefit-risk profile of each opioid drug product, including its risk of abuse, on a case-by-case basis. It is also important to note that FDA takes into consideration available therapies as part of its risk benefit assessment of a drug. This approach is intended to balance the public health interest in the development of drug products with abuse-deterrent properties with the need to preserve access to a range of therapeutic agents (both brand-name and generic) for patients in pain.

In analyzing whether any drug product is safe and effective for its intended use, FDA conducts a benefit-risk analysis of the drug. To provide context for the drug-specific review, FDA considers the severity of the condition that the product is intended to treat, and the benefits and risks of other available therapies for the same condition. For example, Troxyca ER contains a fixed combination of oxycodone and naltrexone, while Xtampza ER contains only oxycodone as an active ingredient. As such, they may have different therapeutic benefits, such as for patients with hepatic impairment which may result in disproportionately higher levels of naltrexone relative to oxycodone.

The science of opioid use, abuse, and abuse deterrence is new and evolving. The agency's evolving scientific understanding of these issues may inform the scope of what drug products the agency considers available therapies, and the benefits and risks of those therapies relative to an opioid drug product under review.