CENTER FOR DRUG EVALUATION AND RESEARCH

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OFFICE DIRECTOR MEMO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

To: **Janet Woodcock, MD**
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Food and Drug Administration (FDA)

From: **Douglas C. Throckmorton, MD**
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Subject: **Abuse-Deterrent Properties of Purdue's Reformulated OxyContin (oxycodone hydrochloride) Extended-Release Tablets**

This memorandum summarizes the complex and technical multidisciplinary review of scientific data regarding Purdue's reformulated OxyContin (oxycodone hydrochloride) extended release tablets[1] (OCR) (NDA 22-272) and its potential abuse deterrent properties for the purposes of regulatory decision-making. This matter has been the subject of extensive consideration by Agency experts over the course of many months. Given the nature of this matter, an integrated assessment of the scientific data and regulatory issues is particularly important.

Accordingly, in my capacity as Deputy Director for Regulatory Programs for the Center for Drug Evaluation and Research (CDER or the Center) -- and given my extensive involvement in scientific and policy decisions on issues related to drugs with abuse potential within CDER -- you have asked me to provide recommendations on the following two issues:

1. Whether the labeling for Purdue Pharma LP's (Purdue's) reformulated OxyContin (oxycodone hydrochloride) extended release tablets (OCR) should be revised to include language describing abuse-deterrent properties of the new formulation along with relevant caveats (the "labeling issue"); and

2. Whether Purdue's original formulation of OxyContin (oxycodone hydrochloride) extended release tablets (OC) should be determined to be withdrawn for reasons of safety or effectiveness (the "relisting issue").

These two issues should be considered in light of the respective standards in the Federal Food, Drug, and Cosmetic Act (the Act) and implementing regulations. FDA has long considered abuse and dependence in different contexts of regulatory decision-making (e.g., product labeling, drug approvals, adverse events).

[1] The approved labeling refers to "OxyContin (oxycodone hydrochloride controlled-release) Tablets."

Fundamental to consideration of both issues here is an overall assessment of potential abuse-deterrent properties of OCR relative to OC. Accordingly, this memo focuses on my assessment of the data regarding those properties. The materials used in preparing this assessment are listed at the end of the document, and consist of extensive scientific reviews of data generated by multiple components of CDER, including the Controlled Substances Staff (CSS), the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP), and the Office of Surveillance and Epidemiology (OSE).

The memorandum concludes by explaining my recommendations on both the labeling issue and the relisting issue. Those recommendations are:

1. That the labeling for OCR should be revised to include language describing the abuse-deterrent properties of the new formulation along with relevant caveats; and

2. That OC should be determined to be withdrawn for reasons of safety or effectiveness.

I. Background

A. Opioids Generally

Prescription opioid analgesics are an important component of modern pain management. Abuse and misuse of these products, however, have created a serious and growing public health problem. FDA has worked to address this problem while ensuring that patients in pain have appropriate access to opioid analgesics. FDA has approved labeling and a risk evaluation and mitigation strategy (REMS) to address the problem of abuse and misuse.

Another important step towards the goal of creating safer opioid analgesics has been the development of opioids that are formulated to deter abuse and misuse. FDA considers the development of these products a high public health priority. Because opioid analgesics must be able to deliver the opioid to patients for the management of pain, the extent to which an abuse-deterrent product is able to reduce misuse and abuse will not be absolute. Therefore, the extent of abuse deterrence can only be understood when studied relative to a comparator.

B. Purdue's OC and OCR

FDA originally approved Purdue's new drug application for OxyContin extended release tablets (OC) (NDA 20-553) on December 12, 1995. The labeling stated that the product should only be taken orally, and warned that taking crushed, chewed, or broken tablets could lead to the rapid release and absorption of a potentially toxic dose of oxycodone. The product was not formulated with properties to deter abuse, and approved labeling did not include language on abuse-deterrent properties.

Purdue subsequently submitted and received approval of another new drug application for reformulated OxyContin extended release tablets (OCR) (NDA 22-272) on April 5, 2010, with the goal of making it more difficult to misuse and abuse by changing the physical and chemical properties of the formulation. The NDA included studies assessing these product attributes. The approved labeling did not include language on abuse-deterrent properties. In addition, as a part of the approval of OCR in 2010, FDA imposed post-marketing requirements to assess the impact of these changes on abuse and misuse patterns in the real world.

Shortly after approval of OCR, Purdue notified FDA by letter dated August 10, 2010, that it had ceased shipment of OC, and FDA subsequently moved OC to the "Discontinued Drug Product List" section of

the "Approved Drug Products With Therapeutic Equivalence Evaluations" (commonly known as the Orange Book). Purdue also asked FDA by letter dated March 19, 2013, to withdraw approval of OC for reasons of safety. There are several pending abbreviated new drug applications (ANDAs) that cite OC as the reference listed drug and propose to duplicate OC. In addition, several citizen petitions have been submitted requesting that FDA determine whether OC (10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, 80 mg, and 160 mg strengths) was voluntarily withdrawn from sale for reasons other than safety or effectiveness.

Purdue submitted data regarding the abuse-deterrent properties of OCR in a citizen petition dated August 28, 2012.[2] On September 14, 2012, Purdue submitted Supplement 014 to NDA 22-272 (S-14) requesting prior FDA approval of labeling describing the abuse-deterrent properties of OCR. The CP and S-014 included data from in vitro, pharmacokinetic (PK), clinical abuse potential and epidemiologic studies.

II. Findings from Multidisciplinary Review

A. Summary of Multidisciplinary Review

FDA evaluated data on the following four categories of abuse-deterrent properties of OCR:[3]

- Laboratory-based in vitro manipulation and extraction studies
- Pharmacokinetics studies
- Clinical abuse potential studies
- Investigations analyzing postmarketing data on abuse

These data have been the subject of extensive evaluation by multiple components of CDER over the course of many months. Key studies discussed in this memo are summarized in the attached chart. Because the extent of abuse deterrence for OCR can best be understood when studied relative to a comparator much of the data compare OC and OCR. The data from all investigations relevant to the potentially abuse-deterrent properties of OCR need to be evaluated together, considering the totality of the evidence, to assess whether and the degree to which OCR can be expected to deter abuse relative to OC.[4]

1. Laboratory-based in vitro manipulation and extraction studies[5]

The goal of these studies was to assess the effects of the new formulation on a variety of in vitro measures related to the manipulation of the formulation for the purposes of abuse and misuse. In other words, the goal is to evaluate the ease with which the potentially abuse-deterrent properties of the formulation can be defeated or compromised. Because the original formulation's extended-release properties were easy to defeat with simple methods such as chewing, one goal was to have the product retain a degree of the extended-release properties after dissolution or extraction of crushed tablets

[2] The petition asked FDA, among other things, not to approve any generic versions of oxycodone hydrochloride extended-release tablets that are not as abuse-deterrent as OCR. FDA issued a non-substantive denial of the petition, which was subject to FDCA 505(q), on January 26, 2013. (Docket FDA-2012-P-0939).

[3] *See* Draft Guidance for Industry: Abuse-Deterrent Opioids — Evaluation and Labeling (January 2013) (hereinafter Draft Guidance) for background on categories of studies that may be relevant for evaluating abuse deterrence.

[4] The evaluation of an abuse-deterrent formulation takes into consideration the most common routes of abuse which in this case are the oral, nasal, and intravenous routes. As reflected in the approved OCR labeling, the use of opioid analgesic products carries the risk of addiction even under appropriate medical use, so it is appropriate to evaluate data on abuse deterrent properties regardless of the population.

[5] See e.g., DAAAP and CSS reviews for more information.

(physical manipulation followed by chemical manipulation or dissolution). Polyethylene oxide (PEO) is the main excipient that imparts these properties. The reformulated OxyContin (OCR) consists of oxycodone hydrochloride in a (b) (4) matrix of (b) (4)

(b) (4)

Important measures of the impact of the new formulation on in vitro properties relevant to abuse are summarized in table one, appended to this review. Several points need to be made about the testing conducted on OCR:

1. The physical chemical testing strategy was driven by the type of abuse deterrent technology being used. If the product had employed a different strategy (e.g., inclusion of an aversive substance to decrease abuse) other testing methods generally would need to be applied.
2. The testing compared OC to OCR to assess relative improvement in the ability to deter abuse or misuse. This type of assessment was necessary because the science of abuse deterrence is relatively new and the ability of physical and chemical properties needed to reduce abuse should be assessed on a case by case basis.
3. The use of repeated measures and, where possible, multiple approaches to physical and chemical manipulation increased the confidence in the validity of the measures.

Overall, the in vitro studies demonstrate that manipulation of OCR tablets is more difficult compared with the manipulation of OC tablets. Compared with the OC formulation, the extended-release mechanism of OCR tablets requires a higher amount of effort, time, experience and tools to defeat making it more difficult to create a fine powder for insufflation. This is important because particle size may influence the rate of opioid release from the manipulated product. For extraction for intravenous abuse, OCR is particularly challenging as it turns into a viscous gel that is resistant to injection. This feature may make abuse via insufflation more difficult also, but whether this is so cannot be measured using mechanical testing methods only and should be considered in the context of the other categories of testing below. Oxycodone in both the OC and OCR formulations is not appropriate for vaporization (e.g., for smoking) as the oxycodone degrades at temperatures close to where vaporization occurs.

To summarize the results, the in vitro data suggests that OCR represents an improvement over OC in that it increases the ability of OCR to resist crushing, breaking, and dissolution. The in vitro data also demonstrate that OCR has physicochemical properties expected to make abuse by injection difficult. The in vitro data provide support, together with other categories of data below, that OCR has physicochemical properties that are expected to reduce abuse via the intranasal route.

2. Pharmacokinetic Studies[6]

The goal of these studies was to assess the effects and better understand the in vivo properties of the new formulation on the release of oxycodone from the formulation, both when intact and following manipulation. The comparison of the intact products was to assure that the OCR formulation is equally bioavailable (when swallowed whole) to the OC formulation. The comparison of the manipulated products was to assess the impact of the new formulation on the abusability of the new formulation

[6] See e.g., DAAAP and CSS reviews for more information.

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