

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

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OFFICE DIRECTOR MEMO



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

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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 tablets¹ (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original formulation of OxyContin (oxycodone hydrochloride) extended release tablets (OC) should be determined to be withdrawn for reasons of safety or effectiveness (the "relisting issue").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 studies⁵

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)}

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 Studies⁶

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.

when taken via known oral and non-oral routes of abuse (i.e., injection, insufflation). For both comparisons, standard pharmacokinetic measures were assessed (including Tmax, Cmax, and AUC).

As summarized in the tables appended to this memo:

1. When serum concentrations of whole OC and OCR were compared, the two formulations are equally bioavailable.
2. When serum concentrations of OC and OCR were compared, both formulations are susceptible to being defeated when chewed vigorously (b) (4), with shorter periods of chewing defeating the OC formulation to a larger degree than the OCR formulation. The result is a longer Tmax for the OCR formulation when chewed routinely compared with OC, which may predict a lower abuse potential.⁷ However, given the ability of chewing to defeat the extended-release features of both formulations, the impact of OCR on oral abuse has yet to be adequately demonstrated.
3. Serum concentrations following crushing of OCR with mortar and pestle show that OCR retains its extended release properties after crushing. In vitro dissolution data following crushing of OC and OCR with mortar and pestle show that crushing by manual means (such as mortar and pestle) defeats the extended-release properties of OC but not OCR tablets.

To summarize the results from this category, the PK and other data demonstrate that (while OCR is as bioavailable as OC), OCR is more resistant than OC to some forms of manipulation but not others. Notably, however, vigorous chewing is still able to disrupt the controlled-release mechanism of the OCR, such that an impact of the formulation change on oral routes of abuse cannot yet be adequately assessed.

3. Clinical Abuse Potential Studies⁸

The goal of these studies was to compare the attractiveness (“likability”) of manipulated OxyContin formulations (OC, OCR) by exposing individuals experienced in the abuse of opioids to these products and assessing their responses.⁹ The focus of these studies was on relevant routes of abuse (particularly insufflation).

As summarized in table three appended to this memo:

1. Finely-crushed and coarsely-crushed OCR had lower liking scores than OC when insufflated. The results were consistent whether evaluated using median liking scores or using a responder analysis.
2. While the full amount of finely- and coarsely-crushed OC could be insufflated by 25 of 27 subjects, only 17 of the 27 subjects tested given OCR were able to insufflate the full amount. OCR and OC caused similar degrees of intranasal irritation.

To summarize the results from this category, the clinical abuse potential studies reinforce data from the other categories of data discussed in this document. The data from the clinical studies, along with

⁷ The Tmax (time to maximum concentration) for the OCR and OC formulations when taken without chewing were 4.5 hours and 2.5 hours, respectively. A longer Tmax has been suggested to be associated with a reduced risk of abuse, but no quantitative link has been established to date.

⁸ See e.g., DAAAP and CSS reviews for more information.

⁹ Clinical abuse potential studies are generally conducted in a drug-experienced abuse population as a common enrichment strategy. These subjects generally are more capable of distinguishing active drug from placebo reproducibly which improves the power of the study to distinguish differences between treatments.

support from the in vitro and other data, indicate that OCR has physicochemical properties that are expected to reduce abuse via insufflation. That is, the reformulation resulted in reduced attractiveness for insufflation of the manipulated OCR to individuals experienced in the abuse of opioids when compared with manipulated OC.

4. Postmarketing Studies¹⁰

The sponsor submitted data from 11 postmarketing investigations, three of which met the characteristics (as set forth in the Draft Guidance) of formal investigations.¹¹ The data from the 11 investigations were reviewed by OSE and DAAAP and the results are summarized in the OSE and DAAAP reviews and in table four appended to this memo. There were three goals of the investigations into the effects of OxyContin reformulation in the real world setting:

1. Compare the rates of abuse, diversion, and outcomes of abuse (e.g., overdose, hospitalization, death) for OCR and OC
2. Compare the rates of adverse events and therapeutic errors for OCR and OC
3. Compare the rates of accidental exposures for OCR and OC

Formal Epidemiologic Studies

These studies submitted by the sponsor assessed the impact of the new OxyContin formulation in several important areas, including overall and route-specific abuse of OCR, OC, and other extended-release oxycodone products. Another study, the Client Treatment Study (CTS) Investigation was submitted to the docket by another company and was also reviewed.

NAVIPPRO™ Study

The NAVIPPRO™ study looked at data from standardized self-administered questionnaires completed by clients entering substance abuse treatment centers to examine the prevalence of OxyContin abuse in the 30 days prior to admission. The results suggested that the replacement of OC with OCR in the marketplace has led to reduced abuse, including reduction of abuse of both OxyContin and other forms of extended-release oxycodone products. These conclusions are limited by the persistence of reported use and abuse of OC long after Purdue had withdrawn OC from marketing.¹² The results of the NAVIPPRO™ study also differ from those reported from the National Survey on Drug Use in Households (NSDUH), which showed no change in non-medical use of OxyContin in the 30 days prior to the interview following replacement of OC with OCR in the marketplace.

¹⁰ See e.g., DAAAP and OSE reviews for more information.

¹¹ The National Addiction Vigilance Intervention and Prevention Program (NAVIPPRO™) Investigation, the Researched Abuse Diversion and Addiction-Related Surveillance (RADARS®) System Poison Center Program (SPCP) Investigation, and the National Poison Data System (NPDS) Investigation.

¹² Current data do not explain the persistence of use of OC. Explanations that have been offered include the persistence of the OC formulation in the supply chain and in patients' homes, as well as mis-identification by individuals of what form of OxyContin they took.

The data from NAVIPPRO™ also suggest an effect of OCR in deterring route-specific abuse. Prior to the introduction of OCR, the rate of non-oral abuse of OxyContin was 70% among abusers. Since the introduction of OCR, the corresponding rate of non-oral abuse of OCR was 40% among abusers.

Client Treatment Study (CTS) Investigation

This study collected information about the routes of abuse of OxyContin in similar ways to NAVIPPRO, collecting data from standardized self-administered questionnaires completed by clients entering substance abuse treatment centers to examine the prevalence of OxyContin abuse. The data from NAVIPPRO™ are in conflict with the data from the CTS. Instead of decreases in the prevalence of overall OxyContin abuse, the CTS reported increases in the prevalence of overall OxyContin abuse in the previous 30 days (via both oral and non-oral routes) from 2.6 to 2.9%.

With regard to route-specific abuse, here again the data from NAVIPPRO do not agree with data from the CTS investigation. In the CTS data, the prevalence of OxyContin abuse via non-oral routes increased from 44 to 48% following OCR introduction. While there are differences in how the data are collected in these two studies and differences in how they were analyzed,¹³ the reason for these different results from similar data sources is not known.

RADARS® System Poison Control Program (SPCP) Investigation

The RADARS data assessed OxyContin abuse by measuring the numbers of poison control calls related to intentional abuse of OxyContin. After the introduction of OCR, there was a 32% decline in call numbers¹⁴. The decline was precipitous after the market introduction of OCR, which was inconsistent with the gradual decline in the numbers of OxyContin prescriptions.

No information about route-specific abuse was obtained.

National Poison Control Data System (NPDS) Investigation

Like RADARS, the NPDS investigation assessed OxyContin abuse by measuring the numbers of poison control calls related to intentional abuse of OxyContin. After the introduction of OCR, there was a 30% decline in call numbers and a 19% decline when the calls were adjusted for the number of prescriptions dispensed for OxyContin. The decline was precipitous after the market introduction of OCR, which was inconsistent with the gradual decline in the numbers of OxyContin prescriptions.

While some of the formal epidemiologic studies suggest a decline in OCR abuse via non-oral routes, other studies do not support such a finding. Longer-term follow-up of the ongoing studies, as well as additional data from other formal studies would be useful.

Additional Post-marketing Investigations

The sponsor conducted additional studies to evaluate the impact of OCR on a variety of outcomes that are plausibly linked to changes in patterns of abuse and misuse.¹⁵ They include information from a variety of relevant sources on the following:

¹³ These differences are discussed in greater detail in the OSE reviews.

¹⁴ Expressed as numbers of calls per unique recipient of an OxyContin prescription.

¹⁵ See reviews from OSE and DAAAP for details.

- Diversion
- Doctor shopping
- Street price of the new OxyContin formulation
- Social use patterns reflected in internet discussions
- Prescribing of OxyContin by physicians identified as ‘high risk’ based on past prescribing patterns.
- OxyContin abuse by abusers followed longitudinally in a cohort of abusers in Kentucky
- Adverse events from sponsor’s International Drug Safety Database (ARGUS).
- Statement of law enforcement personnel involved in enforcement related to prescription drug abuse made to Purdue’s Law Enforcement Liaison and Education trainers from 2010-2012.

Data on Clinical Consequences

While some of the informal studies are designed to assess death related to prescription drug abuse, mortality data are not yet available. To date, the available data from the informal studies, together with the formal epidemiologic studies, are not sufficient to adequately assess the clinical consequences of abuse (e.g., overdose, death, or hospitalizations). Longer-term follow-up of the ongoing studies, as well as additional data from other formal studies and other postmarketing investigations would be useful.

Based on aggregate data from these postmarketing investigations, I believe that while the investigations have some limitations, these data support the findings from other data sources that OCR can be expected to reduce abuse via the intravenous and intranasal routes, and possibly reduce overall abuse.¹⁶ Particularly encouraging data from these sources include the following:

- Declines in prescribing behaviors that have been linked to misuse and abuse: doctor shopping, prescriptions paid for with cash, prescriptions for the highest doses of OxyContin, and prescriptions by physicians identified as ‘high risk’ based on past prescribing patterns.
- Declines in reported rates of insufflation and injection of OCR, and decreases in the average number of days of abuse of OCR via injection or insufflation, compared with OC in a cohort of abusers followed longitudinally in Kentucky.

B. Conclusions from Scientific Multidisciplinary Review

Given the complex, technical, and multidisciplinary nature of this matter, I am including an integrated summary assessment of the scientific data below:

- Both OC and OCR are equally bioavailable when swallowed whole.
- The in vitro data, together with the other data show that, relative to OC, there is an increase in the ability of OCR to resist cutting, crushing, chewing, breaking, and dissolution using a variety of tools and solvents.¹⁷

¹⁶ DAAAP and OSE express consistent views on the more formal postmarketing investigations. Although DAAAP and OSE use different language to characterize the other postmarketing data and have differing views of the robustness of that data, there is general agreement with my conclusions regarding the regulatory implications of the postmarketing data.

¹⁷ OxyContin is also misused for therapeutic purposes. For example, a patient or caregiver may crush the product to administer it if the patient lacks the ability to swallow an intact tablet. As noted in the boxed warning of the labeling, disruption of the tablet and controlled-release mechanism for abuse or misuse “can lead to rapid release and absorption of a

- The in vitro testing of the physical properties of OCR was extensive¹⁸ and rigorously conducted, and the effects shown¹⁹ provide a strong basis for predicting an effect of OCR on route-specific abuse. The studies were appropriate for a formulation that is focused on physical changes to deter abuse and misuse. The testing of the physical properties was robust in that it was also sufficient to reveal how the current formulation could be defeated (e.g., vigorous chewing or robust mechanical grinding).
- The in vitro data, together with the pharmacokinetic data, show that while OCR is more difficult to crush than OC, vigorous chewing is sufficient to defeat the extended-release features of OCR to a similar degree as that seen with OC.²⁰ Accordingly, the impact of the formulation change on the oral route of abuse cannot yet be adequately assessed.
- Intranasal and intravenous opioid abuse are associated with serious adverse events including overdose and death and the OCR can be expected to have a positive public health impact.²¹ Intravenous opioid abuse is associated with HIV and hepatitis B and C infection risk as well as organ damage.²² Intranasal opioid abuse is associated with nasal, palatal, and pharyngeal necrosis.²³
- With regard to intravenous abuse, the in vitro data demonstrate that OCR has physicochemical properties expected to make abuse by injection difficult. When subjected to an aqueous environment, OCR gradually forms a viscous hydrogel (i.e., a gelatinous mass) that resists passage through a needle. The in vitro testing was sufficient to demonstrate that OCR prevents oxycodone from being drawn into a syringe to any meaningful extent. Although there are no supporting pharmacokinetic or clinical data available (and it is not ethically feasible to obtain such data), the in vitro data, coupled with the post-marketing reports, supports the conclusion that OCR has properties that are predicted to reduce abuse by the intravenous route compared with OC.
- With regard to intra-nasal abuse, the clinical studies showed OCR resulted in lower liking scores than OC. The in vitro data also showed that OCR requires a higher amount of effort, time, experience and tools to crush, which could make more difficult the creation of a fine powder for intranasal use. There is also supportive pharmacokinetic and postmarketing data.

potentially fatal dose of oxycodone.” The increased ability of OCR to resist crushing and breaking may have an impact on deterring such use.

¹⁸ For example, the fractionation studies used the full range of particle sizes likely to be achieved for misuse and abuse purposes, and the extraction studies included a broad array of “household”, “industrial,” and pH buffered solvents. The syringeability testing included multiple needle sizes and extraction times and temperatures.

¹⁹ For example, the maximum amount of oxycodone expelled via injection of crushed OCR (through a 27 gauge needle) was (b) (4) as compared with a range of (b) (4) oxycodone expulsion for OC.

²⁰ The pharmacokinetic studies, together with in vitro data, suggest that shorter periods of chewing defeated OC to a larger degree than the OCR formulation, and it is reasonable to conclude that such an effect could have an impact on misuse.

²¹ See Refs. 5-9 (in “Materials Used for This Review”).

²² See Refs. 5-7. According to Section 9.2 of the approved labeling for both OC and OCR, injection of the OxyContin tablet excipients “can result in death, local tissue necrosis, infection, pulmonary granulomas, and increased risk of endocarditis and valvular heart injury.”

²³ See Refs. 8-9.

Based on these data, OCR is predicted to reduce abuse via the intranasal route compared with OC.

- Abuse of OC and OCR is still possible by the intravenous and intranasal routes, as well as by the oral route.
- 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. The difficulty of inhalation is a reflection of properties of the drug substance, not the reformulation.
- The postmarketing data support the conclusions reached using the in vitro, PK, and clinical data, but do not yet demonstrate, a reduction in OCR abuse following replacement of OC with OCR in the marketplace. Additional data, including epidemiological data, when available, will provide further information on the impact of OCR on the abuse liability of the drug.

III. Implications of the Above Assessment for Regulatory Decision-making

The data relevant to the potentially abuse-deterrent properties of OCR need to be evaluated together, considering the totality of the evidence, to assess the implications for regulatory decisions. My recommendations regarding the labeling and relisting issues are discussed below and take into account my assessment of the multidisciplinary review together with applicable standards for evaluating the respective issues. A summary of the salient data considered as a part of this review is included in the tables appended to this document.

A. Labeling Issue

FDA approves an NDA only if the agency determines (among other things) that the drug is “safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling[.]” FDCA 505(b)(1) and (d)(1). An NDA must include “full reports of investigations which have been made to show whether or not such drug is safe for use[.]” FDCA 505(b)(1). FDA may refuse to approve an NDA if:

- The investigations required under section 505(b) of the [FDCA] do not include adequate tests by all methods reasonably applicable to show whether or not the drug is safe for use under the conditions prescribed, recommended, or suggested” in the labeling;
- The results of the tests show that the drug is “unsafe for use under the conditions prescribed, recommended, or suggested” in the labeling or “the results do not show that the drug product is safe for use under those conditions”
- There is insufficient information about the drug to determine whether the product is safe for use under the conditions prescribed, recommended, or suggested” in the labeling.

21 CFR 314.127(b)(2), (3), and (4). An NDA supplement is considered an “application” that must meet the same evidentiary standards for approval as the NDA itself. See 21 CFR 314.3 and 314.71.

FDA has long considered abuse and misuse information a necessary element in evaluating the safety of a drug. For example, if a drug has potential for abuse, agency regulations require NDA and IND sponsors to provide the agency with “a description and analysis of studies or information related to abuse of the drug” and any studies related to overdose. 21 CFR 312.23(a)(10)(i) and 314.50(d)(5)(vii). FDA regulations (in effect since 1985) that require sponsors to review, investigate, and submit to FDA adverse drug experience reports define “adverse drug experience” broadly to

include adverse events occurring from “drug overdose, whether accidental or intentional,” and “drug abuse.” 21 CFR 314.80 and 314.98(a).

A drug’s labeling is approved by FDA as part of the application or supplement. The labeling must be truthful and not misleading, and “must contain a summary of the *essential scientific information* needed for the safe and effective use of the drug.” FDCA 502(a); 21 CFR 201.56(a)(1) (emphasis added). Abuse and misuse information has an established place in drug labeling as “essential scientific information” for safe use. For example, FDA regulations adopted in 2006 require that prescription drug labeling include abuse, dependence, and overdose information, including “the types of abuse that can occur with the drug and the adverse reactions pertinent to them, and must identify particularly susceptible patient populations.” 21 CFR 201.57(c)(10) and (c)(11).

In the Draft Guidance, the agency said that “when the data predict or show that a product’s potentially abuse deterrent properties can be expected to, or actually do, result in a significant reduction in that product’s abuse potential, these data, together with an accurate characterization of what the data mean, should be included in the product labeling.”²⁴ It is important to emphasize that the data relevant to the potentially abuse-deterrent properties of OCR need to be evaluated together, considering the totality of the evidence, to assess whether labeling changes are appropriate. I have considered the totality of the evidence, including in vitro, PK, clinical liking, and post-marketing data, and the robust nature of certain data, as discussed extensively above, and summarized in Section II. I conclude, for purposes of labeling, that the data predict that OCR’s abuse deterrent properties can be expected to result in a significant reduction in OCR’s abuse potential.

Specifically, the in vitro data demonstrate that OCR has physicochemical that are expected to make abuse via injection difficult. In addition, the reduced “liking” shown in the clinical study leads me to conclude that OCR is likely to result in meaningful reductions in intranasal abuse. The clinical study, along with support from the in vitro data, indicate that OCR has physicochemical properties that are expected to reduce abuse via the intranasal route. The in vitro studies and clinical study provide robust support for my conclusions, while the pharmacokinetic and postmarketing investigations are supportive. I recommend that appropriate language be included in the OCR labeling. Inclusion of this information is particularly important because OxyContin has a well-documented history of misuse and abuse, with serious public health consequences.

B. Relisting Issue

A determination regarding whether OC was voluntarily withdrawn from sale for reasons of safety or effectiveness must be made prior to approving an ANDA that refers to it (21 CFR 314.161). Drugs are removed from the list if FDA determines that the listed drug was withdrawn from sale for reasons of safety or effectiveness (FDCA 505(j)(7)(C); 21 CFR 314.162). 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). The agency has recognized that a drug’s safety profile can change

²⁴ See Draft Guidance at 17. The term “significant” in this context of this Draft Guidance is not intended to refer to statistical significance. The comment period on the Draft Guidance recently closed. The agency is currently reviewing the comments it has received and will make changes as appropriate.

due to the availability of alternative products in the context of determining whether a drug was withdrawn for safety or effectiveness reasons.²⁵

FDA has long considered the abuse potential of a drug in numerous regulatory contexts. Where appropriate, FDA may take into account abuse potential as part of the safety profile of a drug when weighing its benefits and risks. In this case, it is appropriate to consider abuse potential as part of the Agency's determination of whether OC was withdrawn from sale for reasons of safety or effectiveness. This approach is particularly appropriate here in light of the extensive and well-documented history of OxyContin abuse.

I have conducted an extensive safety review, and have reached the conclusions discussed above. I have concluded that OC provides the same therapeutic benefits as OCR, but that OC poses an increased potential for abuse by certain routes of administration (i.e., intravenous and intranasal), when compared to OCR. Based on the totality of the available data and information, I have determined that the benefits of OC no longer outweigh its risks. I have also determined that OC was withdrawn from sale for reasons of safety or effectiveness.

Materials Used for This Review

1. Draft Guidance for Industry: Abuse-Deterrent Opioids—Evaluation and Labeling (January 2013).
2. Controlled Substances Staff (CSS) 'Study of Abuse Deterrence Characteristics of Reformulated OxyContin Relative to Original OxyContin' by Michael Klein, Ph.D. dated April 11, 2013.
3. Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) Division Director Review and Medical Officer review of OxyContin data by Robert Rappaport, M.D., and Pamela Horn, M.D. dated April 15, 2013.
4. Office of Surveillance and Epidemiology (OSE) Office-level memorandum on abuse-deterrent formulations of OxyContin by Gerald Dal Pan, MD, dated April 12, 2013.
5. Katz et al, "Tampering with prescription opioids: nature and extent of the problem, health consequences, and solutions," The American Journal of Drug and Alcohol Abuse, vol. 37, pages 205-217.
6. Silva et al, "Factors associated with history of non-fatal overdose among young nonmedical users of prescription drugs," Drug and Alcohol Dependence, vol. 128, pages 104-110.
7. Degenhardt et al, "Mortality among regular or dependent users of heroin and other opioids: a systematic review and meta-analysis of cohort studies," Addiction, vol 106, pages 32-51.
8. CDC, "Integrated prevention services for HIV infection, viral hepatitis, sexually transmitted diseases, and tuberculosis for persons who use drugs illicitly: summary guidance," Morbidity and Mortality Weekly Report, vol. 61, pages 1-40.
9. Alexander et al, "Intranasal hydrocodone-acetaminophen abuse-induced necrosis of the nasal cavity and pharynx," The Laryngoscope, vol. 122, pages 2378-2381.

²⁵ 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 because there is less abdominal fullness and cramping[.]" 76 Fed. Reg. 51037 (Aug. 17, 2011).

Table One: Summary of Physical-Chemical Testing of Reformulated OxyContin (OCR) Compared with Original Formulation OxyContin (OC)

| Property | Test | Results |
|-----------------------------------|---|--|
| Crushability ²⁶ | Distribution of particle sizes after physical manipulation ²⁷ . | <ul style="list-style-type: none"> Original OxyContin formulation (OC) could be crushed into a fine powder using metal spoons. Reformulated OxyContin (OCR) required mechanical means (b) (4) grinder²⁷ to crush tablet to fine powder. |
| Extractability | Release of oxycodone from intact or crushed OC and OCR tablets by extraction using a variety of small volumes of household liquids ²⁸ that can be taken orally as an immediate release solution or injected. | <ul style="list-style-type: none"> Water is effective in extracting oxycodone from crushed and intact OCR and OC. Approximately (b) (4) of the oxycodone hydrochloride in OCR tablets is extracted (b) (4) from finely crushed tablets (b) (4) of oxycodone hydrochloride is extracted from crushed OC tablets (b) (4). (b) (4) were also effective in extracting oxycodone hydrochloride from OCR tablets but to a lesser degree than for extraction from OC tablets. |
| Dissolution | Retention of controlled-release properties after extraction in ethanol and simulated gastric fluids (SGF) ²⁹ . | <ul style="list-style-type: none"> Crushed OCR retains the controlled-release properties, whereas crushed OC releases (b) (4) of oxycodone in (b) (4). (b) (4) Alcohol seems to retard the release of the active ingredient. |
| Syringeability | Filling syringes (b) (4) 27 gauge) after OC and OCR tablets were finely-ground (b) (4). Contents of syringe were then analyzed for oxycodone. | <ul style="list-style-type: none"> OCR is difficult to syringe or inject. The hydro-gelling properties of OCR make it difficult to draw up and what is drawn up has low oxycodone concentrations. By contrast, low volume, highly concentrated aqueous solutions of oxycodone for intravenous use can be readily obtained from OC tablets. |
| Vaporization | Release of oxycodone from ground OC and OCR tablets for the purposes of smoking ³⁰ . | <ul style="list-style-type: none"> The temperature for vaporization of oxycodone hydrochloride is close to the temperature at which oxycodone hydrochloride decomposes making vaporization an ineffective route for oxycodone abuse, either from OCR or OC tablets. |

²⁶ Creation of fine, uniform powder important to insufflation. vaporization or extraction of active ingredients from solid oral dosage formulations. Goal of techniques was the creation of a fine, uniform powder (b) (4)

²⁷ Fifteen household devices, obtained from pharmacies and kitchenware stores, were used in an attempt to fractionate all strengths of OCR and OC tablets. These items were intended to either crush, cut, chop, grate, or grind the tablets. These devices ranged from the simple, such as two metal spoons, to the complex, including a (b) (4) Grinder. Multiple attempts at fractionation were attempted for each device with documentation of both the time and effort required to achieve fractionation.

²⁸ Extractions using standardized methodologies and used liquid including (b) (4)

²⁹ Dissolution tests were conducted (USP Apparatus I) on intact and finely crushed tablets, in simulated gastric fluid without enzyme (SGF), and with (b) (4) ethanol and (b) (4).

³⁰ Inhalation was simulated with (b) (4)

OCR fine powder (b) (4)

Amount of vaporized oxycodone and corresponding amount of residual oxycodone remaining in the analysis tube were monitored.

Table Two: Summary of Pharmacokinetic Testing of Reformulated OxyContin (OCR) Compared with Original Formulation OxyContin (OC)

| Property | Test | Results |
|--|--|---|
| Bioequivalence to original formulation | Oral administration followed by serial serum concentration measurements. | <ul style="list-style-type: none"> OCR meets FDA standards for bioequivalence to OC³¹. |
| Resistance of the controlled-release properties to crushing and other manipulation for oral ingestion | Chewing (usual and vigorous), ³² mechanical crushing | <ul style="list-style-type: none"> Normal chewing defeats controlled-release features of OC and OCR formulations, however longer Tmax of OCR formulation persist (OCR, Tmax median 4.5 h vs. OC Tmax 2.5 h) and a lower Cmax was observed (23.6 % lower when compared to OC) . Vigorous chewing (b) (4) defeats controlled-release features of OC and OCR formulations and the Cmax, AUC and Tmax are similar for both products following oral ingestion Manual crushing (mortar and pestle) defeats the controlled-release features of OC, but does not defeat the controlled-release features of OCR tablets^{33, 34}. Crushing (b) (4) OCR tablets did not change the susceptibility of the formulation to vigorous chewing. |
| Resistance of the controlled-release properties to crushing for intranasal insufflation | Insufflation following mechanical crushing ³⁵ | <ul style="list-style-type: none"> Finely crushed OCR tablets have a longer Tmax and lower Cmax than finely crushed OC³⁶. |

³¹ The ‘area under the curve’ (AUC) is similar for OC and OCR following administration under labeled conditions of use. I note that OCR has a Tmax that is twice as long as that of OC (median Tmax 4.5 h vs. OC Tmax 2.5 h), and that delayed Tmax has been suggested to be associated with reduced abusability. I do not rely on this difference in Tmax to reach the conclusions in my memorandum.

³² The study treatment phases were preceded by a chewing qualification session, where subjects needed to complete a vigorous chewing session with 6 placebo OCR tablets to qualify for the study phases that required harder chewing than normal (vigorous). Under vigorous chewing conditions subjects were instructed to vigorously chew for up to (b) (4) minutes.

³³ After oral ingestion, Tmax, Cmax and AUC are similar for intact and crushed OCR tablets.

³⁴ In vitro dissolution studies in Simulated Gastric Fluid (SGF) (b) (4) showed that manually crushed OC (mortar and pestle, (b) (4) releases over (b) (4) of the active ingredient whereas under the same conditions (b) (4) of the active ingredient is released from the OCR tablets.

³⁵ Finely crushed OCR was generated using (b) (4), whereas the coarsely OCR was obtained with a (b) (4) to be reduced to a (b) (4) pieces. OC, but not OCR, was easily crushed to a fine powder with a mortar and pestle.

Table Three: Summary of Human Abuse Testing of Reformulated OxyContin (OCR) Compared with Original Formulation OxyContin (OC)

| Property | Test | Results |
|---|--|--|
| ‘Likeability’ of OCR formulation when in human abuse studies taken intranasally³⁷ | Insufflation following mechanical crushing. | <ul style="list-style-type: none"> The median Emax for finely crushed OC was significantly larger than that for finely crushed OCR for drug liking on a bipolar “Drug Liking” VAS scale (100 vs. 87). Descriptive statistics showed that approximately 37 % (10 out of 27 subjects) and 55.6 % (15 out of 27 subjects) of subjects in the study had at least a 30 % reduction in drug liking Emax following intranasal administration of finely and coarsely crushed OCR tablets respectively, relative to finely crushed OC³⁸. |
| Other clinical outcomes comparing the OCR and OC formulations taken intranasally | Measures of nasal irritation and measures of completeness of ingestion of dose ³⁹ . | <ul style="list-style-type: none"> No relevant differences in nasal irritation between OCR and OC formulations were detected⁴⁰. Most of the subjects in the trial (25 out of 27) were able to insufflate the full amount of crushed OC, while 10 out of 27 subjects failed to insufflate the full amount of the crushed OCR. |

³⁶ Lower Cmax values were observed for finely and coarsely crushed OCR tablets (LS mean 16.8 ng/mL and 14.5 ng/mL respectively) when compared to OC finely crushed (LS mean 21.7 ng/mL). OC finely crushed had the shorter Tmax: median value 1 hour (Min- Max, 0.25-2.50) versus OCR finely crushed Tmax median of 2 h (Min-Max, 0.75-3.5). OCR, coarsely crushed, had a median of 3 h (Min-Max, 1.00-8.13).

³⁷ Examined in Study OTR-1018.

³⁸ A 30% reduction in ‘liking’ Emax has been suggested as a potential marker for relevant clinical effect.

³⁹ Study OTR-1018 included evaluations of nasal irritation from intranasal administration of each treatment. Assessments of irritation were completed by an Ears, Nose, and Throat (ENT) specialist, using endoscopy and intranasal photography and by each study subject. Assessment by the ENT specialist, conducted approximately 30 minutes post-dosing focused on the categories of nasal congestion, nasal irritation (external), and nasal discharge. The subject rated assessment, conducted at selected times post-dosing focused on the categories of burning, need to blow nose, runny nose/nasal discharge, facial pain/pressure, and nasal congestion.

⁴⁰ Using observer-rated and subject-rated evaluations of nasal irritation. Subject-rated Assessment of Intranasal Irritation [SRAII] and observer-related Assessment of Intranasal Irritation (ORAI) using endoscopy was also conducted as the objective measure of pupillometry.

Table Four: Summary of Post-Marketing Assessment of Abuse of OxyContin, Reformulated OxyContin (OCR), and Original Formulation OxyContin (OC)⁴¹

| Property | Study / Measure | Results |
|---------------|--|--|
| Overall abuse | NAVIPPRO ⁴² / Prevalence of abuse: Past 30-days abuse before vs. after OCR introduction ^{43, 44} | <p>Prevalence⁴⁵ of extended-release (ER) oxycodone abuse statistically significantly decreased among those who reported prescription opioid abuse:</p> <ul style="list-style-type: none"> • Prevalence of any extended-release (ER) oxycodone abuse decreased by (b) (4) from (b) (4) • Prevalence of other ER oxycodone abuse (which includes generic ER oxycodone, Mexican and Canadian OxyContin, and other ER oxycodone) decreased by (b) (4) from (b) (4) • Prevalence of all OxyContin abuse (U.S brand-name formulation only) decreased by (b) (4) from (b) (4) • Prevalence of OC_b and OCR (12.1%) abuse were similar after marketing started for reformulated OxyContin. <p>The prevalence of OCR abuse was 49% lower than the prevalence of OC abuse before marketing started, a statistically significant finding.</p> <p>Among all clients, the prevalence of OxyContin abuse in the past 30 days (regardless of formulation) statistically significantly declined from (b) (4) before, to (b) (4) after OCR introduction</p> |

⁴¹ Focus in this table is on the three formal epidemiologic studies of abuse conducted by Purdue (NAVIPPRO, RADARS System Poison Center Program, and NPDS), and two investigations conducted by Research Triangle Institute (CTS and NSDUH).

⁴² The NAVIPPROTM Investigation, a cross-sectional study, assessed the prevalence of OxyContin abuse in the past 30-days among adults entering a non-random sample of U.S. substance abuse treatment centers, based on standardized intake interviews that incorporated pill cards to identify medications. Route of administration and frequency of abuse (number of days of abuse) were also assessed. Except where noted, the results account for repeat clients admitted to treatment centers. While demographics of NAVIPPROTM clients are similar to demographics among clients entering publicly-funded treatment centers (according to the Treatment Episode Data Set), no data has been submitted on the generalizability of the NAVIPPROTM treatment centers and their clients after applying the investigation’s inclusion/exclusion criteria.

⁴³ Abuse of original OxyContin and other ER oxycodone (e.g., generic ER oxycodone) after marketing started for reformulated OxyContin may confound findings on reformulated OxyContin abuse. Had original OxyContin and other ER oxycodone not been abused after marketing started for reformulated OxyContin, prevalence and frequency of reformulated OxyContin abuse may be higher than reported here.

⁴⁴ An appropriately conducted analysis that incorporates a measure of the availability of the various ER oxycodone formulations has not been performed. Thus, prevalence shown here do not account for the lower number of prescriptions dispensed for ER oxycodone after the introduction of reformulated OxyContin.

⁴⁵ Prevalence calculated here do not account for repeat clients of substance abuse treatment centers. Regarding original OxyContin and reformulated OxyContin, prevalence calculated with and without accounting for repeat patients was similar.

| Property | Study / Measure | Results |
|----------------------|---|--|
| Overall abuse | NAVIPPRO Average days of abuse in past 30-days | <ul style="list-style-type: none"> Frequency of OCR abuse after the introduction of OCR (7.5 days / 30 days) was statistically significantly less than frequency of OC abuse before the introduction (10.75 days / 30 days). |
| Overall abuse | Client Treatment Study Investigation (CTS) ⁴⁶ Prevalence of abuse: past 30 days OxyContin abuse | <ul style="list-style-type: none"> Prevalence of past-30 day OxyContin® abuse statistically significantly increased from 2.6% to 2.9% among all clients. |
| Overall abuse | NSDUH (National Survey on Drug Use in Households) | <ul style="list-style-type: none"> Surveying the prevalence of abuse in a representative sample of non-institutionalized patients, no significant change was seen in the prevalence of past 30-day non-medical OxyContin use after OCR marketing. |
| Overall abuse | RADARS System Poison Center Program ⁴⁷ | <ul style="list-style-type: none"> The mean quarter-year number of intentional abuse exposures to OxyContin was reduced significantly by (b) (4)⁴⁸. |
| Overall abuse | NPDS ⁴⁹ | <ul style="list-style-type: none"> The mean quarter-year number of intentional abuse exposures to OxyContin was reduced significantly by 30%⁵⁰. |
| Route-specific abuse | NAVIPPRO Route-specific past 30-days abuse before vs. after marketing started for reformulated OxyContin | <p>Prevalence of past 30-days abuse before vs. after marketing via oral route of abuse:</p> <ul style="list-style-type: none"> OC: 12.5% before (b) (4) after, a statistically significant relative percent change OCR: 9.0% <p>Prevalence of route-specific past 30-days abuse before vs. after marketing via non-oral route of abuse:</p> <ul style="list-style-type: none"> OC: 18.1% before (b) (4) after, a statistically significant relative percent change OCR: 4.8% |

⁴⁶ Commissioned by (b) (4) and submitted by Research Triangle Institute.

⁴⁷ The Researched Abuse Diversion and Addiction-Related Surveillance (RADARS) System Poison Control Center Program Investigation, a cross-sectional study, assesses the extent of OxyContin abuse by measuring the number of poison control center calls related to intentional abuse of OxyContin from a non-random sample of poison control centers in the US.

⁴⁸ When adjusted for the number of recipients of OxyContin the reduction was 32%, a finding that remained statistically significant.

⁴⁹ The National Poison Data System (NPDS) Investigation, a cross-sectional study, assesses the extent of OxyContin abuse by measuring the number of poison control calls related to intentional abuse and misuse of OxyContin from all US regional poison control centers.

⁵⁰ When adjusted for the number of OxyContin prescriptions dispensed, the reduction was 19%, a finding that was not statistically significant.

| Property | Study / Measure | Results |
|---------------------------------------|---|---|
| Route-specific abuse | NAVIPPRO Routes of abuse profile: Percent of those reporting OxyContin abuse via specific routes of administration, among those reporting OxyContin abuse | Abuse of OCR was more via oral route, with less non-oral abuse, than abuse of OC: <ul style="list-style-type: none"> • Among those who abused OC, approximately 55% reported abuse via oral routes, and approximately 70% reported abuse via non-oral routes. • Among those who abused OCR, approximately 75% reported abuse via oral routes, and approximately 40% reported abuse via non-oral routes. |
| Route-specific abuse | Client Treatment Study Investigation (CTS) | <ul style="list-style-type: none"> • Among clients who abused OxyContin®, the percent reporting usually abusing OxyContin® via non-oral routes of administration also statistically significantly increased from 44% to 48%. |
| Clinical consequences of abuse | Potential metrics: deaths, overdoses, overdose, and rates of addiction | <ul style="list-style-type: none"> • No study findings on clinical consequences of abuse were submitted for Purdue’s formal studies of abuse (NAVIPPRO, RADARS System Poison Center Program and NPDS). |

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/s/

DOUGLAS C THROCKMORTON
04/16/2013