DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: 03/03/2015

TO: OxyContin Controlled-Release Tables (NDA 022272) File

FROM: CDER Exclusivity Board

SUBJECT: Three-Year Exclusivity Recommendation for OxyContin (oxycodone hydrochloride) Controlled-Release Tablets (NDA 022272, S014)

SUMMARY

This memo addresses whether the report of an abuse potential study submitted by Purdue Pharma, L.P. ("Purdue") in supplement S014 (S-14) to new drug application (NDA) 022272 for OxyContin (oxycodone hydrochloride) controlled-release tablets approved on April 16, 2013, would qualify this supplement for 3-year exclusivity under sections 505(c)(3)(E)(iv) and 505(j)(5)(F)(iv) of the Federal Food, Drug, and Cosmetic Act ("FD&C Act"). The relevant abuse potential study, a "drug liking" study, supported the addition of information to the labeling indicating that OxyContin has physical and chemical properties that are expected to reduce abuse via the intranasal route (snorting).

Upon review of regulatory documents related to S-14 and discussions with the Division of Anesthesia, Analgesia, and Addiction Products (the Division), the Exclusivity Board (the Board) within the Center for Drug Evaluation and Research (CDER) recommends that the Agency recognize 3-year exclusivity for OxyContin based on the report of the drug liking study supporting the supplement, and that an exclusivity code be assigned that reflects the narrow scope of this exclusivity.

A discussion of the Board's reasoning follows.

I. FACTUAL AND PROCEDURAL BACKGROUND

Purdue Pharma, L.P. (Purdue) submitted NDA 022272 on November 29, 2007, for a reformulated version of its previously approved OxyContin (oxycodone HCl) controlled-release

tablets (NDA 020553).[1] According to Purdue, the "reformulated OxyContin" (OCR) had controlled-release features that would be less easily compromised by tampering than the "original OxyContin" (OC), and thereby result in a reduction in abuse. Specifically, the formulation changes were intended to create a tablet that was more difficult to crush or dissolve, and more resistant to the extraction of oxycodone by chemical means. After several review cycles, OCR was approved on April 5, 2010, for the same indication as OC, namely "the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time." No new clinical studies were performed − or required − to support the original approval of OCR because comparative pharmacokinetic studies showed that OCR and OC had comparable bioavailability.[2] The approved labeling at the time did not provide any specific information regarding the abuse-deterrent properties of OCR.

Among other post-marketing requirements, the Agency required that Purdue conduct epidemiological studies to address whether the formulation changes incorporated in OCR that were intended to provide misuse and abuse-deterrence actually result in a decrease in misuse and abuse, and their consequences: overdose, death and addiction.[3] In other words, any epidemiological study (or studies) had to assess the impact of the reformulation on the abuse of OxyContin in the community.

On September 14, 2012, Purdue submitted S-14 to NDA 022272 requesting FDA approval of labeling describing the abuse-deterrent properties of OCR. S-14 included data from *in vitro* manipulation and extraction, pharmacokinetic, clinical abuse potential (drug liking), and epidemiologic studies relevant to the potentially abuse-deterrent properties of OCR.[4] The drug-liking study supporting the approval of S-14, OTR 1018, was a pivotal, single-center, randomized, double-blind, positive- and placebo controlled, 5-treatment crossover study in non-dependent, recreational opioid users to evaluate the abuse potential, pharmacokinetics, and safety of intranasally administered finely and coarsely crushed OCR versus original OC and oxycodone active pharmaceutical ingredient.[5] Purdue also submitted supportive safety data from an intranasal tolerability study.[6]

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[1] NDA 020553 was approved on December 12, 1995. The product was not formulated with properties to deter abuse, and approved labeling did not include language on abuse-deterrent properties. 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.

[2] The NDA also consisted of CMC data, non-clinical pharmacology studies and studies that assessed the attributes of the reformulation in terms of the effects of chemical and physical manipulation intended to defeat the modified-release characteristics of the product.

[3] Medical Officer Review, NDA 022272, November 12, 2012 (Medical Officer Memo), at 4.

[4] Office Director Memo, NDA 022272, April 16, 2013, (Office Director Memo), at 3.

[5] Office Director Memo at 5.

[6] The intranasal tolerability study, OTR 1022, was a single-center, randomized, single-blind, single-dose, six sequence, triple-treatment, triple-period crossover study in non-dependent, recreational opioid users to evaluate the pharmacokinetics, tolerability, and safety of intranasally administered OCR, both finely crushed and coarsely, as well as finely crushed OC. Although the PK results of OTR 1022 were consistent with those observed in OTR 1018, the study was less informative than OTR 1018. It did not, for instance, include an evaluation of drug liking, and thus the PK findings could not be correlated to drug-liking measures. With respect to intranasal tolerability, the study indicated that while the formulations of both OCR and OC caused mild irritation, the effects of their non-active components were not expected to be a deterrent to intranasal abuse (Medical Officer Review at 11). CDER's Controlled Substances Staff did not consider this study in its evaluation of OCR's abuse deterrence properties (Memo from Michael Klein, Director, Clinical Substances Staff (CSS) to Douglas Throckmorton, Deputy Director,

The data from all these studies were evaluated together, and the totality of the evidence was assessed to determine whether, and the degree to which, OCR could be expected to deter abuse relative to OC.[7] S-14 was approved on April 16, 2013, with labeling describing the risks specific to the abuse of OxyContin, the results of the abuse deterrence studies (both *in vitro* manipulation/extraction and clinical), and the summary conclusions reached from such studies about the abuse-deterrent properties of the drug in Section 9.2 (Abuse & Deterrence) of the labeling(See Appendix A for labeling changes approved in S-14). Specifically, the labeling states that "[t]he data from the clinical study [the drug liking study], along with support from the *in vitro* data, also indicate that OxyContin has physicochemical properties that are expected to reduce abuse via the intranasal route."[8]

II. STATUTORY AND REGULATORY BACKGROUND

The availability of a 3-year exclusivity period for a supplement to an NDA is described in sections 505(c)(3)(E)(iv) and 505(j)(5)(F)(iv) of the FD&C Act. The statute states:

> If a supplement to an application approved under subsection (b) of this section . . . contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the supplement and conducted or sponsored by the person submitting the supplement, the Secretary may not make the approval of an application submitted under subsection (b) of this section for a change approved in the supplement effective before the expiration of three years from the date of the approval of the supplement under subsection (b) of this section if the investigations described in clause (A) of subsection (b)(1) of this section and relied upon by the applicant for approval of the application were not conducted by or for the applicant and if the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted.[9]

Thus, the standard under the FD&C Act for determining whether a supplement to an NDA for a drug containing a previously approved active ingredient is eligible for 3-year exclusivity is that the approval of the supplement be supported by clinical investigations that are: (1) new, (2) not bioavailability studies, (3) essential to approval, and (4) conducted or sponsored by the applicant. If any one of the four requirements is not met, then the supplement is not eligible for 3 years of exclusivity. FDA's regulation on 3-year exclusivity mirrors the statutory framework.[10]

Under applicable regulations, a "clinical investigation" means "any experiment other than a bioavailability study in which a drug is administered or dispensed to, or used on, human subjects."[11] For purposes of exclusivity determinations, the Agency interprets the phrase "new

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CDER, April 11, 2013), and the approved labeling for OCR does not contain any information from this study. Accordingly, OTR 1022 will not be addressed further in this memorandum.

[7] Office Director Memo at 11.

[8] OxyContin approved labeling, Section 9.2 (Abuse & Deterrence).

[9] Sections 505(c)(3)(E)(iv); see also section 505(j)(5)(F)(iv).

[10] 21 CFR 314.108(b)(5).

[11] 21 CFR 314.108(a).

clinical investigations" in the 3-year exclusivity statutory provisions to mean an investigation conducted on humans "the results of which have not been relied on by FDA to demonstrate substantial evidence of effectiveness of a previously approved drug product for any indication or of safety for a new patient population and do not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness or safety in a new patient population of a previously approved drug product."[12] In the preamble to implement the exclusivity provisions of the Hatch-Waxman Act (proposed rule), FDA indicated that a clinical investigation need not be adequate and well-controlled or meet the "standard of substantial evidence" to serve as the basis for conferring exclusivity.[13] Instead, the Agency's interpretation of the term "clinical investigation" is that "it be of the type necessary to support approval of the proposed change."[14] Moreover, the Agency has also clarified that for purposes of exclusivity, "data from a clinical investigation previously submitted for use in the comprehensive evaluation of the safety of a drug product but not to support the effectiveness of the drug product would be considered new."[15]

An investigation is conducted or sponsored by the person submitting the supplement if "before or during the investigation, the applicant was named in Form FDA-1571 filed with FDA as the sponsor of the investigational new drug application under which the investigation was conducted or the applicant or the applicant's predecessor in interest provided substantial support for the investigation."[16]

In addition, the Agency interprets the phrase "essential to approval" to mean that "with regard to an investigation . . . there are no other data available that could support approval of the application." [17] In the preamble to its final exclusivity regulations (the final rule), FDA explained that to meet this standard, a clinical investigation must be "vital" to the application or supplement and there must not be any published studies (other than the applicant's) or other information available to FDA that would allow the Agency to approve the proposed drug product as safe and effective.[18] In other words, the application or supplement could not be approved without the investigation.

III. DISCUSSION

The drug-liking study, OTR 1018, qualifies as a "clinical investigation" because it is a human study (and not a bioavailability study) in which a drug (OCR) is dispensed to and used by human subjects, and is of the type necessary to support approval of the labeling change proposed in S-

[12] *Id.*
[13] Abbreviated New Drug Applications, Proposed Rule, 54 Fed. Reg. 28872, 28899 (July 10, 1989).
[14] *Id.*
[15] Abbreviated New Drug Applications; Patent and Exclusivity Provisions, Final Rule, 59 Fed. Reg. 50338, 50369 (Oct. 3, 1994).
[16] 21 CFR 314.108(a).
[17] 21 CFR 14.108(a).
[18] 59 Fed. Reg. 50338, 50357 (Oct. 3, 1994). See also FDA's Exclusivity Summary in which the Agency further explains that an investigation is not considered essential to approval if there is other information that would be sufficient to provide approval of the change (such as what is already known about a previously approved product or from published literature or other public information that would have supported the change approved in the application).

14, i.e., the addition of information to Section 9.2 of the labeling indicating that the product has physical and chemical properties that are expected to reduce abuse via the intranasal route (snorting). This clinical investigation is "new" for the purpose of exclusivity because it was not previously relied upon by the Agency to support a finding of safety and/or efficacy of any application,[19] and is "essential to the approval" because there are no other data available to support approval of this supplement.[20] Accordingly, S-14 satisfies the standards for 3-year exclusivity.

The issues before the Board in this instance are the scope of exclusivity and the assignment of an appropriate exclusivity code in the Orange Book that best characterizes this exclusivity.

Exclusivity extends only to the change approved in the supplement for which new clinical investigations were essential, and the Agency interprets the scope of 3-year exclusivity to be related to the scope of the underlying new clinical investigations that were essential to the approval of the supplement. As discussed above, OTR 1018 did not support approval of the original NDA 022272 on April 5, 2010, and was thus not essential to the approval of the specific abuse-deterrent formulation of OCR. This study only supported the addition of information obtained from the drug liking study to the OCR labeling that indicates that OCR has physicochemical properties that are expected to reduce abuse via the intranasal route.[21] Therefore, the scope of exclusivity in this instance is limited to the addition of this information to Section 9.2 in the labeling.

The Board notes generally that the scope of exclusivity should be determined by the nature of the clinical studies done to gain approval of the NDA, not by the exclusivity code that is used as shorthand to describe that approval in the Orange Book. Nevertheless, the Board recommends that when the Orange Book listing is updated to display this exclusivity period, OCR be assigned a unique exclusivity code that reflects the scope of this exclusivity. Given that the scope of 3-year exclusivity in this instance is limited to the addition of information to the OCR labeling regarding the reduction of abuse via the intranasal route, the Board recommends that the following exclusivity code be assigned:

> M-###:[22] "Addition of Information Regarding the Intranasal Abuse Potential of OxyContin."

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[19] Purdue submitted a final study report for clinical study OTR 1018 under IND 29,038 on September 16, 2010, well after NDA 022272 was first approved (Memo from James Tolliver, CSS, to Michael Klein & Silvia Calderon, September 21, 2012, at 1). The study period for OTR 1018 ran from January 11, 2010 (the date the first subject was enrolled) to April 8, 2010 (the date the last subject was completed) (OTR1018 Final Clinical Study Report, Section 2 (Synopsis) at 1). These dates indicate that Study OTR 1018 was incomplete at the time NDA 022272 was first approved on April 5, 2010, and thus could not have supported approval of that application. Moreover, a review of the application history did not show that any interim data from this study had been provided, or was reviewed, to support approval of NDA 022272.

[20] S-14 supports the approval of labeling to specifically include data from Study OTR 1018. Moreover, according to the Division, no other data exists to support approval of this supplement.

[21] Office Director Memo at 11; see also Division Director Review, NDA 022272, April 15, 2013, at 1-2.

[22] Under the Agency's long term practice, exclusivity codes with an "I" prefix ("I-###") are suggestive of new indication exclusivity, exclusivities for "new dosing schedules" are assigned a "D-###" code, whereas exclusivities that do not neatly fall into either of these two categories are assigned a "miscellaneous" use code "M-###."

This exclusivity will expire on April 16, 2016, 3 years from the date that S-14 was approved.

APPENDIX A:
ADDITIONS TO SECTION 9.2 (ABUSE & DETERRENCE) SUPPORTED BY S-14

Risks Specific to Abuse of OxyContin

OxyContin is for oral use only. Abuse of OxyContin poses a risk of overdose and death. Abuse may occur by taking intact tablets in quantities greater than prescribed or without legitimate purpose, by crushing and chewing or snorting the crushed formulation, or by injecting a solution made from the crushed formulation. The risk of overdose or death is increased with concurrent use of OxyContin with alcohol and other central nervous system depressants. Taking cut, broken, chewed, crushed, or dissolved OxyContin enhances drug release and increases the risk of overdose and death.

With parenteral abuse, the inactive ingredients in OxyContin can result in death, local tissue necrosis, infection, pulmonary granulomas, and increased risk of endocarditis and valvular heart injury. Parenteral drug abuse is commonly associated with transmission of infectious diseases, such as hepatitis and HIV.

Abuse Deterrence Studies

OxyContin is formulated with inactive ingredients intended to make the tablet more difficult to manipulate for misuse and abuse. For the purposes of describing the results of studies of the abuse-deterrent characteristics of OxyContin resulting from a change in formulation, in this section, the original formulation of OxyContin, which is no longer marketed, will be referred to as "original OxyContin" and the reformulated, currently marketed product will be referred to as OxyContin.

In Vitro Testing

In vitro physical and chemical tablet manipulation studies were performed to evaluate the success of different extraction methods in defeating the extended-release formulation. Results support that, relative to original OxyContin, there is an increase in the ability of OxyContin to resist crushing, breaking, and dissolution using a variety of tools and solvents. The results of these studies also support this finding for OxyContin relative to an immediate-release oxycodone. When subjected to an aqueous environment, OxyContin gradually forms a viscous hydrogel (i.e., a gelatinous mass) that resists passage through a needle.

Clinical Studies

In a randomized, double-blind, placebo-controlled 5-period crossover pharmacodynamic study, 30 recreational opioid users with a history of intranasal drug abuse received intranasally administered active and placebo drug treatments. The five treatment arms were finely crushed OxyContin 30 mg tablets, coarsely crushed OxyContin 30 mg tablets, finely crushed original OxyContin 30 mg tablets, powdered oxycodone HCl 30 mg, and placebo. Data for finely crushed OxyContin, finely crushed original OxyContin, and powdered oxycodone HCl are described below.

Drug-liking was measured on a bipolar drug liking scale of 0 to 100 where 50 represents a neutral response of neither liking nor disliking, 0 represents maximum disliking and 100 represents maximum liking. Response to whether the subject would take the study drug again was also measured on a bipolar scale of 0 to 100 where 50 represents a neutral response, 0 represents the strongest negative response ('definitely would not take drug again') and 100 represents the strongest positive response ('definitely would to take drug again').

Twenty-seven of the subjects completed the study. Incomplete dosing due to granules falling from the subjects' nostrils occurred in 34% (n=10) of subjects with finely crushed OxyContin, compared with 7% (n=2) of subjects with finely crushed original OxyContin and no subjects with powdered oxycodone HCl.

The intranasal administration of finely crushed OxyContin was associated with a numerically lower mean and median drug liking score and a lower mean and median score for take drug again, compared to finely crushed original OxyContin or powdered oxycodone HCl as summarized in Table 2.

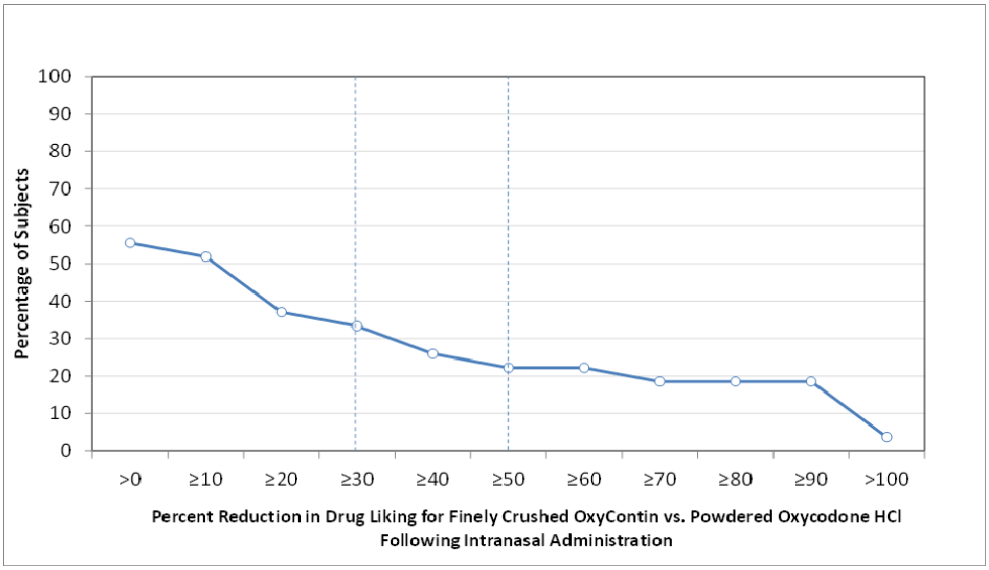
Table 2. Summary of Maximum Drug Liking (E_{max}) Data Following Intranasal Administration

VAS Scale (100 mm)*		OxyContin (finely crushed)	Original OxyContin (finely crushed)	Oxycodone HCl (powdered)
Drug Liking	Mean (SE)	80.4 (3.9)	94.0 (2.7)	89.3 (3.1)
	Median (Range)	88 (36-100)	100 (51-100)	100 (50-100)
Take Drug Again	Mean (SE)	64.0 (7.1)	89.6 (3.9)	86.6 (4.4)
	Median (Range)	78 (0-100)	100 (20-100)	100 (0-100)

*** Bipolar scales (0 = maximum negative response, 50 = neutral response, 100 = maximum positive response)**

Figure 1 demonstrates a comparison of drug liking for finely crushed OxyContin compared to powdered oxycodone HCl in subjects who received both treatments. The Y-axis represents the percent of subjects attaining a percent reduction in drug liking for OxyContin vs. oxycodone HCl powder greater than or equal to the value on the X-axis. Approximately 44% (n = 12) had no reduction in liking with OxyContin relative to oxycodone HCl. Approximately 56% (n = 15) of subjects had some reduction in drug liking with OxyContin relative to oxycodone HCl. Thirty-three percent (n = 9) of subjects had a reduction of at least 30% in drug liking with OxyContin compared to oxycodone HCl, and approximately 22% (n= 6) of subjects had a reduction of at least 50% in drug liking with OxyContin compared to oxycodone HCl.

Figure 1: Percent Reduction Profiles for Emax of Drug Liking VAS for OxyContin vs. oxycodone HCl, N=27 Following Intranasal Administration



The results of a similar analysis of drug liking for finely crushed OxyContin relative to finely crushed original OxyContin were comparable to the results of finely crushed OxyContin relative to powdered oxycodone HCl. Approximately 43% (n = 12) of subjects had no reduction in liking with OxyContin relative to original OxyContin. Approximately 57% (n = 16) of subjects had some reduction in drug liking, 36% (n = 10) of subjects had a reduction of at least 30% in drug liking, and approximately 29% (n= 8) of subjects had a reduction of at least 50% in drug liking with OxyContin compared to original OxyContin.

Summary

The *in vitro* data demonstrate that OxyContin has physicochemical properties expected to make abuse via injection difficult. The data from the clinical study, along with support from the in vitro data, also indicate that OxyContin has physicochemical properties that are expected to reduce abuse via the intranasal route. However, abuse of OxyContin by these routes, as well as by the oral route is still possible.

Additional data, including epidemiological data, when available, may provide further information on the impact of the current formulation of OxyContin on the abuse liability of the drug. Accordingly, this section may be updated in the future as appropriate.

OxyContin contains oxycodone, an opioid agonist and Schedule II controlled substance with an abuse liability similar to other opioid agonists, legal and illicit, including fentanyl, hydromorphone, methadone, morphine, and oxymorphone. OxyContin can be abused and is subject to misuse, addiction, and criminal diversion *[See Warnings and Precautions (5.1) and Drug Abuse and Dependence (9.1)]*.

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/s/

LISA E BASHAM
03/07/2015