DEC 2 0 2018

Edwin R. Thompson, President
Pharmaceutical Manufacturing Research Services, Inc.
202 Precision Road
Horsham, PA 19044

RE: Docket No. FDA-2016-P-0645

Dear Mr. Thompson:

This letter responds to the citizen petition submitted to the Food and Drug Administration (FDA or the Agency) by Pharmaceutical Manufacturing Research Services, Inc. (PMRS) and received on February 22, 2016 (Petition). Your Petition requests that FDA change its approach to evaluating abuse-deterrent formulations and labeling for opioid drug products, including by incorporating changes to the final guidance for industry entitled *Abuse-Deterrent Opioids – Evaluation and Labeling Guidance* (Evaluation and Labeling Guidance). Your Petition further requests that FDA take certain actions regarding OxyContin (oxycodone hydrochloride (HCl) controlled-release tablets) marketed under new drug application (NDA) 22272 (Reformulated OxyContin) and OxyContin (oxycodone HCl controlled-release tablets) marketed under NDA 20553 (Original OxyContin).

Specifically, PMRS requests that FDA take the following actions:

(i) Apply the existing standards for laboratory-based in vitro manipulation and extraction studies, including both *small* and *large* volume extraction, before permitting opioid drug products with potentially abuse deterrent properties to be approved;

(ii) Remove Category 3 human abuse-deterrent (liking) studies from the [Evaluation and Labeling] Guidance and as a requirement for approval of drug products with potentially abuse deterrent properties as inherently flawed, subjective, and highly prone to manipulation;

(iii) Require post-marketing empirical proof through epidemiological or other scientifically rigorous studies that shows that opioid drug products with potentially abuse deterrent properties do in fact result in a meaningful reduction in misuse, abuse, addiction, overdose and/or death before approving abuse deterrent labeling for opioid drug products and before permitting opioid drug products to be marketed as abuse deterrent;

(iv) Require that all opioid drug products currently labeled abuse deterrent be required to meet the standards set forth in (i)-(iii) or have their abuse deterrent labeling removed within a reasonable period of time not to exceed six months. In particular, as shown [in the Petition], because the current Reformulated OxyContin cannot meet these standards,

the FDA should take immediate actions for the reasons stated in [A Proactive Response to Prescription Opioid Abuse][1] to:

(a) Revoke the abuse deterrent labeling from Reformulated OxyContin as approved under New Drug Application 022272 and supplement S014. The in vitro data relied upon by the FDA to approve abuse deterrent labeling is insufficient based on scientific principles and standards. For example, the FDA failed to require and evaluate abuse by small volume extraction. The "liking" study relied upon by the FDA was determined to be subjective, and to not meet the required CFR standard of adequate, well-controlled, robust, rugged and scientifically rigorous testing and the standards in the [Evaluation and Labeling] Guidance for Industry. Post-marketing epidemiology data clearly establishes that Reformulated OxyContin has no meaningful abuse deterrent effects.

(b) Revoke retroactively the three year grant of exclusivity to Purdue for Reformulated OxyContin. The "liking" study relied upon by the FDA was determined to be subjective and does not meet the required CFR standard of adequate, well-controlled, robust, rugged and scientifically rigorous testing and the standards in the Guidance for Industry.

(c) Restore NDA No. 020553 for original OxyContin. The in vitro data relied up on by the FDA to find that Reformulated OxyContin has a meaningful abuse deterrent effect over original OxyContin is insufficient. For example, the FDA failed to require and evaluate abuse by small volume extraction. The "liking" study relied upon by the FDA was determined to be subjective and to not meet the required CFR standard of adequate, well-controlled, robust, rugged and scientifically rigorous testing and the standards in the Guidance for Industry. Postmarketing epidemiology clearly establishes that Reformulated OxyContin has no meaningful abuse deterrent effects.

Petition at 3-4.

We have carefully considered your Petition and the supplement to your Petition dated August 25, 2016 (Supplement). For the reasons explained below, your Petition is denied.

I. BACKGROUND

A. FDA's Efforts to Address the Opioid Crisis

The Petition highlights the rise in opioid abuse, addiction, and overdose deaths. We share your concerns about this national crisis. The Agency has taken significant steps to address this crisis, such as expanding the Risk Evaluation and Mitigation Strategy (REMS) that had applied to extended-release/long-acting opioid analgesics to include immediate-release (IR) products[2] and

[1] Califf, Robert M., Woodcock, J., Ostrolff, S., (2016), A Proactive Response to Prescription Opioid Abuse, New England Journal of Medicine.

[2] FDA News Release, FDA takes important steps to encourage appropriate and rational prescribing of opioids through final approval of new safety measures governing the use of immediate-release opioid analgesic medications, September 30, 2018, available at https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm620935.htm.

our efforts to curb illegal online sales of unapproved opioids.[3] These are just two examples of the many efforts FDA has undertaken to address opioid abuse, addiction, and overdose deaths.[4] One component of the Agency's broader strategy to combat the opioid crisis has been to support the development of opioid products with abuse-deterrent properties. On January 14, 2013, FDA announced the availability of the draft guidance for industry *Abuse-Deterrent Opioids—Evaluation and Labeling*.[5] Among other things, the draft guidance provided recommendations as to how the potentially abuse-deterrent properties of an opioid analgesic formulated to deter abuse should be studied, specifically addressing in vitro studies, pharmacokinetic (PK) studies, clinical abuse potential studies, and postmarketing studies. The draft guidance also described the types of information that may be suitable for inclusion in labeling. Following issuance of the draft guidance, FDA held a public meeting on October 30-31, 2014, during which participants discussed the development, assessment, and regulation of abuse-deterrent formulations of opioid medications.[6]

The Agency carefully reviewed and considered the comments it received on the draft guidance, including comments provided at the public meeting, when developing the final version of the guidance, the availability of which was announced in the *Federal Register* on April 2, 2015.[7] Among other changes, the final guidance clarified that more destructive and/or severe manipulation methods are not needed for in vitro studies once the abuse-deterrent property has been defeated. In addition, the concept of "Tiers" of labeling claims described in the draft guidance was revised to "Categories" based on the categories of study data, to avoid implying that these different types of data exist on a rigid hierarchy in relation to one another. The final guidance recommends that, in most cases, to obtain a full and scientifically rigorous understanding of the impact of a technology or technologies on a product's abuse potential, data from each of following three categories of premarket studies are appropriate: (1) laboratory-

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[3] FDA News Release, FDA takes action against 53 websites marketing unapproved opioids as part of a comprehensive effort to target illegal online sales, June 5, 2018, available at https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm609869.htm.

[4] See Timeline of Selected FDA Activities and Significant Events Addressing Opioid Misuse and Abuse, available at https://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm338566.htm.

[5] *Draft Guidance for Industry on Abuse-Deterrent Opioids–Evaluation and Labeling*; Availability (78 FR 2676, January 14, 2013).

[6] *Development and Regulation of Abuse-Deterrent Formulations of Opioid Medications*; Public Meeting (79 FR 56810, September 23, 2014).

[7] *Guidance for Industry on Abuse-Deterrent Opioids–Evaluation and Labeling*; Availability (80 FR 17765, April, 2, 2015). We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Guidances Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. FDA also issued a final guidance for industry entitled *General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products* (November 2017), which recommends studies, including comparative in vitro studies, that should be conducted to demonstrate that a proposed generic solid oral opioid drug product is no less abuse-deterrent than its reference listed drug. Because your request focuses on the Evaluation and Labeling Guidance (e.g., your request to remove Category 3 studies from the Evaluation and Labeling Guidance) and the NDA approvals for Reformulated OxyContin and Reformulated Opana, we interpret your request to be directed to NDAs of abuse-deterrent opioid formulations and not generic versions of abuse-deterrent opioid products (i.e., a new opioid drug product for which approval is sought in an abbreviated new drug application submitted under section 505(j) of the FD&C Act) (21 U.S.C. 355(j)).

based in vitro manipulation and extraction studies (Category 1); (2) PK studies (Category 2); and (3) clinical abuse potential studies (Category 3).[8] The guidance also provides recommendations related to postmarket (Category 4) studies, which are intended to determine whether the marketing of a product with abuse-deterrent properties results in meaningful reductions in abuse, misuse, and related adverse clinical outcomes in the post-approval setting.[9]

FDA has continued to support efforts to better understand the impact of products with abuse-deterrent properties in the post-approval setting, and to seek public input on the current data and methods for evaluating these products and ways to improve them. For example, the Agency convened a public workshop on these topics in July 2017.[10]

B. Original and Reformulated OxyContin

Your petition makes several requests related to OxyContin. FDA approved NDA 20553 for Original OxyContin, held by Purdue Pharma L.P. (Purdue), on December 12, 1995.[11] 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.[12]

Purdue reformulated the product with physicochemical properties intended to make the tablet more difficult to manipulate for purposes of abuse or misuse and submitted a new application for Reformulated OxyContin. The Agency approved Reformulated OxyContin on April 5, 2010, but the approved labeling did not include statements about its abuse-deterrent properties.[13] Purdue submitted data regarding the abuse-deterrent properties of Reformulated OxyContin in a citizen petition dated August 28, 2012.[14] On September 14, 2012, Purdue submitted a supplement (S-014) to NDA 22272 seeking FDA approval of labeling describing the abuse-deterrent properties of Reformulated OxyContin. The citizen petition and supplemental NDA included data from in vitro, PK, clinical abuse potential, and epidemiologic studies.

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[8] See Evaluation and Labeling Guidance at 5.

[9] Id. at 17.

[10] Data and Methods for Evaluating the Impact of Opioid Formulations with Properties Designed to Deter Abuse in the Postmarket Setting: A Scientific Discussion of Present and future Capabilities; Public Workshop; Issues paper; Request for Comments, available at https://www.fda.gov/Drugs/NewsEvents/ucm540845.htm.

[11] NDA 20553 approval letter (December 12, 1995), available at http://www.accessdata.fda.gov/drugsatfda_docs/appletter/pre96/020553ltr.pdf.

[12] Office Director Memorandum from Douglas C. Throckmorton, Deputy Director for Regulatory Programs, CDER, to Janet Woodcock, Director, CDER (Office Director Memorandum), dated April 16, 2013, at 2, available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/022272Orig1s014ODMemo.pdf.

[13] NDA 022272 approval letter (April 5, 2010), available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022272s000Approv.pdf; see also Labeling for Reformulated OxyContin (April 5, 2010), available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022272lbl.pdf.

[14] See docket FDA-2012-P-0939, available through https://www.regulations.gov.

FDA's extensive review of the data led to a determination that, when compared to Original OxyContin, Reformulated OxyContin has an increased ability to resist crushing, breaking, and dissolution using a variety of tools and solvents, based on premarket assessments.[15] The data also demonstrate that when subjected to an aqueous environment, Reformulated OxyContin gradually forms a viscous hydrogel.[16] With regard to intranasal abuse, clinical studies showed that Reformulated OxyContin resulted in lower liking scores than Original OxyContin.[17] Based on these data, the Agency concluded that the physicochemical properties of Reformulated OxyContin are expected to make abuse via injection difficult and are expected to reduce abuse via the intranasal route. The Agency also determined that the postmarketing data supported the conclusions reached using the in vitro, PK, and clinical data, but do not yet demonstrate, a reduction in Reformulated OxyContin abuse following replacement of Original OxyContin in the marketplace.[18]

On April 16, 2013, FDA approved supplement S-014 to NDA 22272, which added a description of Reformulated OxyContin's abuse-deterrent properties to its labeling. This approved labeling states that "relative to original OxyContin, there is an increase in the ability of [Reformulated] OxyContin to resist crushing, breaking, and dissolution using a variety of tools and solvents."[19] The labeling also notes that "[w]hen subjected to an aqueous environment, [Reformulated] OxyContin gradually forms a viscous hydrogel (i.e., a gelatinous mass) that resists passage through a needle."[20] With respect to insufflation, the labeling states that "[t]he intranasal administration of finely crushed [Reformulated] OxyContin was associated with a numerically lower mean and median liking score and a lower mean and median score for take drug again, compared to finely crushed original OxyContin or powdered oxycodone HCl . . . ."[21]

In correspondence dated August 12, 2010 Purdue notified FDA that it had ceased shipment of Original OxyContin, and FDA subsequently moved Original OxyContin to the "Discontinued Drug Product List" section of FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations*, commonly known as the Orange Book. In April 2013, FDA announced its determination that Original OxyContin was withdrawn from sale for reasons of safety or effectiveness because, although Original OxyContin had the same therapeutic benefits as Reformulated OxyContin, Original OxyContin posed an increased potential for abuse by certain routes of administration when compared to Reformulated OxyContin.[22] Therefore, based on the totality of the data and information available to the Agency at the time, FDA concluded that the

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[15] Office Director Memorandum, at 8, available.

[16] Id. at 9.

[17] Id.

[18] Id. at 10.

[19] DRUG ABUSE AND DEPENDENCE, *Controlled Substance*, Reformulated OxyContin labeling (April 16, 2013), available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022272Orig1s014lbl.pdf.

[20] Id.

[21] Id.

[22] Determination That the OXYCONTIN (Oxycodone Hydrochloride) Drug Products Covered by New Drug Application 20-553 Were Withdrawn From Sale for Reasons of Safety or Effectiveness (78 FR 23273, April 18, 2013).

benefits of Original OxyContin no longer outweighed its risks.[23] Purdue voluntarily requested that approval of the application for Original OxyContin be withdrawn and waived its opportunity for a hearing. FDA withdrew approval of the application for Original OxyContin under section 505(e) of the Food, Drug, and Cosmetic (FD&C) Act (21 U.S.C. 355(e)) in August 2013.[24]

C. Original and Reformulated Opana

In discussing OxyContin, the Petition compares features of that product and its approval history to that of Opana ER. On June 22, 2006, FDA approved Opana ER (oxymorphone HCl extended-release (ER) tablets (NDA 21610)) (Original Opana) held by Endo Pharmaceuticals Inc. (Endo).[25] The approved labeling for Original Opana stated that the product should be swallowed whole and warned that crushing, chewing, snorting, or injecting the product will result in uncontrolled delivery of the opioid and pose a significant risk to the abuser that could result in overdose and death.[26] The approved labeling for Original Opana did not include statements about abuse-deterrent properties.

On December 9, 2011, FDA approved a reformulated version of Opana, also called Opana ER (oxymorphone HCl ER tablets (NDA 201655)) (Reformulated Opana).[27] The NDA for Reformulated Opana included data from studies designed to assess the abuse-deterrent properties of the new formulation.[28] Reformulated Opana consisted of oxymorphone hydrochloride embedded in a polyethylene oxide matrix, which was intended to make the product more difficult to misuse and abuse. The NDA for Reformulated Opana included data from in vitro and in vivo studies designed to assess the abuse-deterrent properties of the new formulation. Although FDA approved the application in December 2011 because it concluded that Reformulated Opana was safe and effective, the Agency did not approve labeling describing abuse-deterrent properties because the Agency concluded that the available data were inadequate to support such labeling.[29]

Endo notified FDA by mail in May 2012 that it voluntarily removed Original Opana from sale, and on August 10, 2012, Endo submitted a citizen petition asking FDA to determine that

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[23] Id. at 23274.

[24] Purdue Pharma L.P; Withdrawal of Approval of a New Drug Application for Oxycontin (78 FR 48177, August 7, 2013).

[25] NDA 021610 approval action letter (June 22, 2006), available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2006/021610s000_021611s000_Approvable.pdf.

[26] WARNINGS, *Misuse, Abuse and Diversion of Opioids*, Original Opana labeling, available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2006/021610s001,021611s001lbl.pdf.

[27] NDA 201655 approval letter (December 9, 2011), available at http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2011/201655Orig1s000Ltr.pdf.

[28] See, e.g., Division Director Summary Review (January 7, 2011, Ref. ID: 28888730), available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/201655Orig1s000MedR.pdf.

[29] Opana ER Briefing Document at 13, available at https://wayback.archive-it.org/7993/20170404143350/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM545762.pdf.

Original Opana was withdrawn from sale for safety reasons.[30] On February 15, 2013, Endo submitted a supplement (S-009) to NDA 201655 seeking FDA approval of labeling describing Reformulated Opana's abuse-deterrent properties. In support of the supplemental NDA, Endo submitted: (1) the same studies on which it had previously sought to rely, which FDA had previously found inadequate by themselves; and (2) preliminary post-marketing data.[31] Endo withdrew the supplement on August 11, 2016.[32]

On May 10, 2013, FDA responded to the citizen petition by denying the petition and determined that Original Opana was not withdrawn from sale for reasons of safety or effectiveness.[33] The Agency concluded that while there is an increased ability of Reformulated Opana to resist crushing relative to Original Opana, study data indicated that Reformulated Opana's extended-release features could be compromised when subjected to other forms of manipulation, such as cutting, grinding, or chewing, followed by swallowing.[34] The Agency also concluded that Reformulated Opana could be readily prepared for injection, and it also appeared that Reformulated Opana could be prepared for snorting using commonly available tools and methods.[35] Finally, the Agency found that the postmarketing studies were inconclusive, and even if one were to treat the available data as a reliable indicator of abuse rates, one of these studies suggested the troubling possibility that a higher percentage of Reformulated Opana abuse was via injection than was the case with Original Opana.[36]

FDA concluded that while Reformulated Opana and Original Opana have the same therapeutic benefits, there was insufficient evidence that Original Opana had an increased potential for abuse compared to Reformulated Opana.[37] Accordingly, FDA determined that the benefits of Original Opana continued to outweigh its risks, and thus, Original Opana was not withdrawn from sale for reasons of safety or effectiveness.[38] As a result, generic versions of Original Opana could continue to be approved and marketed. On June 19, 2013, the Agency issued a notice in the *Federal Register* of this determination.[39]

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[30] Endo Pharmaceuticals Inc Citizen Petition (August 10, 2012, FDA-2012-P-0895), available at https://www.regulations.gov/document?D=FDA-2012-P-0895-0001.

[31] Open Session Background Document: Regulatory History of Opana ER (February 1, 2017), at 67, available at https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM545760.pdf.

[32] Id.

[33] FDA/CDER Final Response to Endo Pharmaceuticals Inc Petition Denial (May 10, 2013, FDA-2012-P-0895), available at https://www.regulations.gov/document?D=FDA-2012-P-0895-0014.

[34] Id. at 5.

[35] Id. at 6.

[36] Id.

[37] Id. at 8.

[38] Id.

[39] Determination That OPANA ER (Oxymorphone Hydrochloride) Drug Products Covered by New Drug Application 21-610 Were Not Withdrawn From Sale for Reasons of Safety or Effectiveness (78 FR 38053, June 25, 2013).

On March 13-14, 2017, FDA's Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) and its Drug Safety and Risk Management (DSaRM) Advisory Committee held a joint meeting to discuss safety issues concerning Reformulated Opana.[40] The majority of the committee members found that the totality of the evidence showed a shift in the abuse pattern of Reformulated Opana from the nasal to injection route of abuse following the product's reformulation. The committees also found that the injection abuse of Reformulated Opana was likely associated with a serious outbreak of human immunodeficiency virus (HIV) and hepatitis C in Indiana, as well as thrombotic thrombocytopenic purpura (TTP)-like illnesses in Tennessee and elsewhere.[41] The committees concluded by a vote of 18-8 that the benefits of Reformulated Opana no longer outweighed its risks.

On June 8, 2017, based on a review of the postmarketing data and consideration of the advice from the March 2017 AADPAC and DSaRM joint meeting, FDA requested that Endo remove Reformulated Opana from the market. Following FDA's request, Endo announced in July 2017 that it would voluntarily remove Reformulated Opana from the market.

II. DISCUSSION

The following sections of this letter discuss the requests in your Petition and FDA's responses to those requests. In Section II.A-C of this letter, we address your request that the Agency change how it evaluates and approves abuse-deterrent formulations and labeling. In Section II.D of this letter, we respond to your claim that the Agency's approval of Reformulated OxyContin's abuse-deterrent properties labeling was in error, and to your request that FDA require the removal of Reformulated OxyContin's abuse-deterrent labeling claims, revoke the three-year grant of exclusivity to Purdue for Reformulated OxyContin, and "restore" the NDA for Original OxyContin. As explained further below, your requests are denied.

A. Require Manipulation and Extraction Studies for Abuse-Deterrent Formulations, Including Both Small and Large Volume Extraction

You request that FDA "[a]pply the existing standards for laboratory based in vitro manipulation and extraction studies, including both small and large volume extraction, before permitting opioid drug products with potential abuse-deterrent properties to be approved" (Petition at 3, 20).

In general, FDA believes that it is appropriate for applicants to provide data from small-volume syringeability and large-volume extraction studies in certain circumstances (e.g., when the proposed labeling makes claims that the opioid product has physicochemical properties expected to make abuse via injection difficult). Every opioid product with FDA-approved labeling describing properties expected to deter abuse via the intravenous route has been supported by

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[40] See Summary Minutes of the DSaRM and AADPAC Joint Meeting, March 13-14, 2017, available at https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM551226.pdf.

[41] TTP is a rare but serious blood disorder characterized by macroangiopathic hemolytic anemia and thrombocytopenia.

small-volume syringeability and large-volume extraction studies.[42]

Although we have generally found that conducting small-volume syringeability and large-volume extraction studies is appropriate in the case of products with potential for abuse by injection, we decline to impose a blanket requirement that all opioid drug products with potentially abuse-deterrent properties be evaluated using such studies, regardless of the route of abuse they are intended to deter or the specific characteristics of the formulation. As stated in the Evaluation and Labeling Guidance, "[t]he data necessary to support abuse-deterrent labeling will depend on the characteristics of the product that impart the abuse deterrence and the route of abuse."[43] For instance, we may encounter a product with novel abuse-deterrent properties for which small-volume syringeability and large-volume extraction studies may not necessarily be the best method to evaluate the product's abuse-deterrent features. Accordingly, your request that the Agency always require small-volume syringeability and large-volume extraction studies before approving any opioid drug products with potentially abuse-deterrent properties is denied. We will continue to evaluate each application on a case-by-case basis, based on the totality of the evidence.[44]

B. Remove Category 3 Studies from the Evaluation and Labeling Guidance

You request that FDA "[r]emove Category 3 human abuse-liability (liking) studies from the [Evaluation and Labeling] Guidance and as a requirement for approval of drug products with potentially abuse-deterrent properties as inherently flawed, subjective, and highly prone to manipulation" (Petition at 3).[45] You also suggest that Category 3 studies lack the scientific rigor required of clinical investigations under 21 CFR 314.126 (Petition at 5; 16-18). Citing §314.126 ("Adequate and well-controlled studies"), you state that the Evaluation and Labeling Guidance "does not eliminate or waive the statutory requirement that studies supporting FDA approvals be robust, rugged and scientifically rigorous" (Petition at 5).

We disagree that Category 3 studies are inherently flawed, subjective, or prone to manipulation. As with Category 1 and Category 2 studies, the design of Category 3 studies should be scientifically rigorous. The Evaluation and Labeling Guidance states that "the preferred design [for Category 3 studies] is a randomized, double-blind, placebo-controlled and positive controlled crossover study" and encourages applicants to use a pre-qualification phase "to increase the power of [the] study to detect differences in the abuse potential of the various

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[42] The Petition asserts that FDA approved abuse-deterrent labeling for Reformulated Oxycontin in the absence of small-volume extraction studies. (Petition at 12). As explained in section II.D.1, this is incorrect.

[43] Evaluation and Labeling Guidance at 23.

[44] Because the science of abuse deterrence is relatively new, and the formulation technologies and methods for evaluating those technologies are rapidly evolving, the Agency takes a flexible and adaptive approach to the evaluation and labeling of abuse-deterrent products. Evaluation and Labeling Guidance at 2. This approach also reflects the fact that FDA expects applicants to take advantage of technological improvements to update their formulations and to allow labeling statements related to abuse deterrence to be commensurate with those advances. Id. at 23.

[45] Category 3 studies are also referred as human abuse liability (HAL) or human abuse potential (HAP) studies.

formulations of drug and placebo."[46] It further recommends that "[t]he potential abuse-deterrent product should be compared to a positive control, and the positive control should be compared to placebo to validate the study."[47] Study subjects should be carefully selected, and the studies should be conducted in opioid-experienced recreational drug users who have experience with the particular route of abuse being studied.[48] The study design should include a selection of routes of administration based on epidemiological data that show that the selected routes are relevant.[49] The final guidance also discusses which standardized instruments (e.g., Visual Analogue Scales (VAS), Profile of Mood States) are appropriate for measuring the subjective responses predictive of the likelihood of abuse and how Category 3 studies should be validated.[50] A statistical analysis plan should be included in the study protocol or submitted as a separate document before un-blinding the study, and the statistical analysis of the data should begin with descriptive statistics making up tabulations and graphs that include tables of the mean, standard error, and other summary statistics.[51] These measures, as outlined in the Evaluation and Labeling Guidance, help ensure that Category 3 studies are scientifically rigorous.

You state that "[t]he [Evaluation and Labeling] Guidance recognizes that 'liking' studies are subjective and lack rigor" (Petition at 6), which is incorrect. The Evaluation and Labeling Guidance discusses how Category 3 studies can be used to measure study subjects' *subjective responses* that can predict the likelihood of abuse; it does not suggest that the studies themselves are subjective, unreliable, or lacking in rigor. As support for your claim, you state that "[t]he [Evaluation and Labeling] Guidance notes that 'nonclinical drug discrimination studies are useful in the evaluation of the abuse potential of a drug, **but their utility in predicting the impact of abuse-deterrent properties on human behavior has not been established**'" (Petition at 6, citing Evaluation and Labeling Guidance at 14, emphasis added in Petition). The "nonclinical drug discrimination studies" mentioned in the Evaluation and Labeling Guidance do not refer to Category 3 studies, which are clinical studies using human subjects. Rather, the Evaluation and Labeling guidance uses this phrase to refer to animal models used to evaluate the abuse potential of drug substances.[52] The use of animal models in nonclinical drug discrimination studies is described in detail in the separate guidance for industry, *Assessment of Abuse Potential of Drugs*.

Category 3 studies constitute an integral component in the premarket assessment of abuse

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[46] Evaluation and Labeling Guidance at 10-11.

[47] Id. at 11.

[48] Id. at 11-12.

[49] Id. at 12.

[50] Id. at 13.

[51] Id.

[52] This section of the Evaluation and Labeling Guidance discusses other studies (in addition to Category 1, 2, and 3 studies) that can be used to assess the impact of an abuse-deterrent formulation on actual abuse, such as Category 4 studies and nonclinical drug discrimination studies. Id. at 5.

deterrence.[53] These studies are important because they can demonstrate the impact of a specific abuse-deterrent feature on a proposed product's abuse potential by assessing the reported "drug-liking" of the test product drug following manipulation compared with a placebo and with the positive control, which is generally the non-abuse-deterrent comparator following manipulation. Category 3 studies help assess recreational drug users' preferences between the abuse-deterrent formulation, placebo, and positive control. We believe that this data further supports a determination that a formulation can be expected to deter abuse in the real world.

As noted above, the Agency generally recommends that applicants conduct studies from all three premarket study categories to support abuse-deterrent labeling claims, and the Evaluation and Labeling Guidance notes that in general "any development program for studying abuse-deterrent technologies should include data from all three categories of studies . . . ."[54] The guidance further states that "[i]n general, most abuse-deterrent information included in product labeling will be based on data from more than one category."[55] It is through the combined use of all three categories of premarket studies, when applicable given the formulation and route of abuse being studied, that the Agency is best able to accurately assess a product designed to have abuse-deterrent properties and can evaluate the formulation's expected impact on abuse in the community. The Agency has concluded that Category 3 studies can provide important evidence relevant to this assessment. Accordingly, your request to remove Category 3 studies from the Evaluation and Labeling Guidance is denied.

C. Require Postmarketing Evidence That the Abuse-deterrent Formulation has Resulted in a Meaningful Reduction in Abuse

You request that FDA require "post-marketing empirical proof through epidemiological or other scientifically rigorous studies that shows that opioid drug products with potentially abuse deterrent properties do in fact result in a meaningful reduction in misuse, abuse, addiction, overdose and/or death before approving abuse deterrent labeling for opioid drug products and before permitting opioid drug products to be marketed" (Petition at 4). You state that the Agency should withhold approval of "abuse deterrent labeling until post-marketing studies in fact establish conclusively the [abuse-deterrent] properties of a particular drug formulation" (Petition at 20).

Your Petition suggests that FDA should initially approve opioid drug products designed to have abuse-deterrent properties based on premarket studies, without labeling claims highlighting any abuse-deterrent properties. Applicants would then be required to generate "post-marketing empirical proof in the field of abuse deterrence" (Petition at 1) before any labeling statements regarding abuse-deterrent properties would be approved.

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[53] HAP studies provide information on the relative abuse potential of a test drug in humans. Data from these studies are used by FDA to formulate controlled substance scheduling recommendations to the Drug Enforcement Agency (DEA). Id. at 9-10.

[54] Evaluation and Labeling Guidance at 5.

[55] Evaluation and Labeling Guidance at 23.

The two-step approach you describe—with labeling regarding abuse-deterrent properties being approved only if, and after, postmarket evidence of deterrence becomes available—is in contrast to that currently recommended in the Evaluation and Labeling Guidance. Notably, though, the guidance contemplates a stepwise approach to evaluation of products with properties intended to deter abuse, reflecting the distinct role of premarket and postmarket evidence. The guidance explains that "premarket studies are intended to demonstrate properties that are *predictive* of a meaningful abuse-deterrent effect" for one or more routes of administration (emphasis added).[56] The guidance further states that:

> When premarket data show that a product's abuse-deterrent properties can be expected to result in a meaningful reduction in that product's abuse, these data, together with an accurate characterization of what the data mean, should be included in product labeling. When postmarket data become available that demonstrate a meaningful reduction in abuse by one or more routes of administration, these data should be added to the product labeling.[57]

Recognizing that postmarket data may provide important insight on the impact of abuse-deterrent properties on abuse in the real world, FDA has required postmarket studies to evaluate the impact of those properties in the post-approval setting for all opioids with abuse-deterrent labeling claims.[58] Although Reformulated OxyContin was initially approved by FDA without labeling describing its properties expected to deter abuse, as discussed above, FDA believes the approach currently recommended in our Evaluation and Labeling Guidance is preferable to the approach recommended in your Petition for several reasons.

First, our extensive work reviewing studies of multiple abuse-deterrent opioid formulations leads us to conclude that the data generated in Category 1, 2, and 3 premarket studies provide an acceptable scientific basis to predict that a formulation can be expected to deter abuse by one or more routes. Key to this is the fact that each category of study provides important, but different, information on the potential abuse-deterrent properties of the formulation. In particular, Category 1 in vitro studies are designed to evaluate the ease with which a product can be manipulated for purposes of abuse.[59] Category 2 studies generally compare the PK profile of the manipulated formulation with the intact formulation and with manipulated and intact formulations of comparator drugs through one or more routes of abuse, with the goal of understanding the in vivo properties of the formulation.[60] Category 3 studies, as described above, are generally conducted to assess how much the manipulated abuse-deterrent formulation is "liked" as compared to manipulated formulations of the comparator drug and placebo.[61] Taken together, the

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[56] Evaluation and Labeling Guidance at 22.

[57] Id.

[58] See FDA Overview Slides (Slide 9) for Day 1 (July 10, 2017) Public Meeting, Data and Methods for Evaluating the Impact of Opioid Formulations with Properties Designed to Deter Abuse in the Postmarket Setting: A Scientific Discussion of Present and Future Capabilities, available at https://www.fda.gov/downloads/Drugs/NewsEvents/UCM565981.pdf.

[59] Evaluation and Labeling Guidance at 6.

[60] Id. at 8.

[61] Id. at 9-11.

data from the three categories of premarket studies can provide a sound scientific basis for concluding that a product's formulation can be expected to deter abuse.

Second, your Petition does not provide a compelling reason why abuse-deterrent labeling should not be approved based on premarket studies. The Petition's objection to abuse-deterrent labeling based on premarket data stems from concerns over the lack of small-volume syringeability studies and the "subjective" nature of Category 3 studies, which have been addressed above. Your Petition also suggests that approving abuse-deterrent labeling based on premarket data may encourage physicians to prescribe abuse-deterrent formulations based on the mistaken belief that these products have absolute abuse-deterrent properties (Petition at 20). We agree that it is important that abuse-deterrent claims are clear and would not lead to misinterpretation. However, we do not agree that eliminating claims based on a potential for misunderstanding would be preferable to FDA's current approach, which we believe provides for labeling statements that are appropriately tailored to the evidence upon which they are based. In particular, the Prescribing Information (PI) of opioid products approved with abuse-deterrent labeling contains language intended to ensure the labeling does not overstate the product's abuse-deterrent properties. For example, the Abuse subsection of the PI for Morphabond ER (morphine sulfate) extended-release tablets states as follows:

> The in vitro data demonstrate that MORPHABOND ER has physiochemical properties expected to make abuse via injection difficult. The data from the clinical study, along with support from in vitro data, also indicate that MORPHABOND ER has physicochemical properties that are expected to reduce abuse by the intranasal route of administration. However, abuse by intranasal, intravenous, and oral routes is still possible.
>
> Additional data, including epidemiological data, when available, may provide further information on the impact of the current formulation of MORPHABOND ER on the abuse liability of the drug. Accordingly, this section may be updated in the future as appropriate.[62]

This carefully crafted language is consistent with the position articulated in the Evaluation and Labeling Guidance, which makes clear that "abuse-deterrent does not mean abuse-proof" and that "labeling should reflect a product's abuse-deterrent properties, as supported by the data, but should include a caveat that abuse is still possible."[63]

We note that the Agency is undertaking a study to improve its understanding of prescriber beliefs relating to use of opioid products with abuse-deterrent properties.[64] The Agency is evaluating currently-used nomenclature for such products, including by surveying doctors to better understand how they perceive terms like "abuse-deterrent" and to assess the clinical

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[62] DRUG AND DEPENDENCE, *Abuse*, Morphabond labeling (September 18, 2018), available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/206544s008s010lbl.pdf

[63] Evaluation and Labeling Guidance at 22.

[64] See Scott Gottlieb, M.D., Commissioner of Food and Drugs, Remarks Delivered Before FDA's Scientific Meeting on Opioids (Jul. 10, 2017), available at https://www.fda.gov/newsevents/speeches/ucm566189.htm.

understanding that has developed around products with labeling for abuse-deterrent properties. However, we do not currently have information that would lead us to conclude that the language used in the approved labeling of these products is inappropriate or misleading, and your Petition contains no such information.

Third, we believe your proposed two-step approach—in which postmarket evidence of abuse deterrence would be required before abuse-deterrent claims could be included in labeling—could result in less research on abuse-deterrent technologies and fewer marketed products with abuse-deterrent formulations. One reason for this involves the challenges presented by conducting and interpreting relevant postmarket studies with the currently available data and methods. These challenges include a lack of data on abuse or overdose involving specific products and routes of abuse in most data sources, substantial product misclassification, inconsistent or unvalidated outcome definitions, sampling bias, and difficulty distinguishing changes in abuse rates that are due to the abuse-deterrent formulation from those due to other interventions or trends in drug abuse patterns.[65] In addition, the market uptake of most abuse-deterrent opioid products is low, which makes it difficult to test for meaningful differences in abuse rates between the abuse-deterrent formulation and an appropriate comparator opioid product in postmarket settings.[66] Consequently, as stated in the Evaluation and Labeling Guidance, "data on the impact of an abuse-deterrent product on drug abuse in the U.S. population are limited[.]"[67] FDA believes it will take time for the data and methods to develop in the area of postmarket studies regarding the impact of abuse-deterrent properties. Because of this, the Agency has yet to approve labeling stating that a product has been shown to reduce abuse in the community. Given these limitations in available postmarket data, we believe the approach you propose could significantly delay, or entirely preclude, inclusion of scientifically sound information regarding abuse deterrence in product labeling, while increasing uncertainty for applicants seeking to develop new technologies to deter abuse.

Thus, we do not believe it would be appropriate to require postmarket data to support abuse-deterrent labeling claims in the way that you suggest. Instead, approving abuse-deterrent labeling claims based on premarket studies, which we believe provide an adequate scientific basis to conclude that a product can be expected to deter abuse, provides prescribers with important information about differences between available therapies. As explained above, the Agency believes that making such products available as an option for prescribers is in the public interest.

Therefore, for the reasons described in parts A, B, and C of this section we decline to adopt the approach described in your Petition.

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[65] See generally, Issues Paper, Data and Methods for Evaluating the Impact of Opioid Formulations with Properties Designed to Deter Abuse in the Postmarket Setting (FDA-2017-N-2903).

[66] FDA's Current Approach to the Postmarket Evaluation of Opioid Analgesic Products with Properties Intended to Deter Abuse, RADARS annual meeting (May 10, 2018), at 11-14, available at https://www.radars.org/system/events/RADARS%20System%202018%20Annual%20Meeting_Meyer.pdf.tmp.

[67] Evaluation and Labeling Guidance at 17.

We therefore deny your requests above (Sections II.A-C), and your request that FDA remove abuse-deterrent claims from the labeling of those opioid drug products already approved that you assert do not meet your requested standards.

D. Revise Labeling for Reformulated OxyContin to Remove the Abuse-deterrent Claims, Revoke the Three-year Exclusivity, and Restore Original OxyContin to the Market

You request that FDA "revoke the abuse deterrent labeling from Reformulated OxyContin," "revoke retroactively the three year grant of exclusivity to Purdue for Reformulated OxyContin," and "restore NDA No. 020553 for original OxyContin" (Petition at 4). In support of your request, you claim that the Agency "failed to require and evaluate abuse by small volume extraction," that "Reformulated OxyContin provides no significant abuse deterrence to the primary known route of abuse," that "[t]he 'liking study relied upon by the FDA was determined to be subjective, and to not meet the required CFR standard[s]," and that the "post-marketing epidemiology data clearly establishes that Reformulated OxyContin has no meaningful abuse deterrent effects" (Petition at 4, 13). You further state that due to these alleged deficiencies, Reformulated OxyContin is misbranded because it lacks the abuse-deterrent properties described in the labeling (Supplement at 2). We do not agree with your claims and, for the reasons set forth below, we deny your requests.

1. Claim that the Agency Failed to Require and Evaluate Small-volume Extraction/Syringeability Studies for Reformulated OxyContin

Your Petition asserts that studies conducted to assess deterrence of intravenous abuse for Reformulated OxyContin were inadequate. In particular, you state that "[w]ithout explanation, the FDA failed to test [Reformulated OxyContin] for abuse by small volume extraction" (Petition at 11). You claim that FDA was aware of the potential for abuse by small volume extraction because the Agency "denied abuse deterrent labeling for [Opana] based, in part, on the fact that the oxymorphone can be extracted from [the product's] formulations in high yields and high purity via small volume extraction." (Petition at 11).

In fact, approval of labeling for Reformulated Oxycontin was supported by small volume extraction studies. As discussed in a memorandum dated April 11, 2013 prepared by the Controlled Substance Staff (CSS) for the FDA Center for Drug Evaluation and Research (CDER), Purdue submitted data from several in vitro studies in response to a Complete Response letter dated October 3, 2008, regarding Purdue's proposed reformulation of OxyContin under NDA 22272.[68] The memorandum explains that Purdue submitted data from these studies to demonstrate that the physical properties of the product's formulation are more difficult to abuse by non-oral routes. As noted in the memorandum, these studies are summarized in a 2013 paper published in the journal *Drug and Alcohol Dependence*, which includes a detailed discussion of the small-volume extraction/syringeability studies that Purdue conducted on Reformulated

[68] CSS Memorandum (April 11, 2013, Reference ID: 3292186) (CSS Memorandum) at 1, available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/022272Orig1s014OtherR.pdf.

still possible."[73] We believe that, generally speaking, if an opioid product is shown through scientifically rigorous testing to have properties expected to deter abuse by snorting and injection, this is important information to provide to prescribers through labeling, even if the product has not been shown, or is not expected, to deter abuse by the oral route (following chewing or otherwise).

Furthermore, while not relevant to Reformulated OxyContin because its labeling does not include a reference to properties that can be expected to deter abuse by the oral route, FDA has emphasized that *abuse-deterrent* is not the same as *abuse-proof*, and the fact that a product has FDA-approved labeling describing abuse-deterrent properties does not mean the product is impossible to abuse or that these properties necessarily prevent overdose and death.[74] Because the FDA-approved labeling for Reformulated OxyContin does not include statements regarding deterrence of oral abuse, the methodology for and the results of Purdue's studies evaluating the oral route of abuse are not relevant to Reformulated OxyContin's approved abuse-deterrent labeling claims.[75]

3. Claim That the Category 3 Study for OxyContin is Subjective and Lacks Scientific Rigor

You state that "'liking' study OTR1018 cannot support a meaningful abuse deterrent effect because the 'liking' study is subjective and lacks scientific foundation" (Petition at 16). Study OTR1018, a Category 3 study, was a single-center, double-blind study in non-dependent, recreational opioid users to evaluate the abuse potential, PK, and safety of intranasally administered coarsely and finely crushed Reformulated OxyContin when compared against finely crushed Original OxyContin, powdered oxycodone active pharmaceutical ingredient (API), and placebo. As explained in Section II.C of this letter, we do not agree that Category 3 studies are subjective or lack scientific rigor.[76]

You state that study OTR1018 is flawed because "[t]here is no statistical or meaningful difference between 'liking' the '-finely crushed' [Reformulated OxyContin] versus the

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[73] Abuse subsection of the DRUG ABUSE AND DEPENDENCE section of the labeling for Reformulated OxyContin available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/022272s039lbl.pdf.

[74] See, e.g., FDA Facts: Opioid Medications, available at http://www.fda.gov/NewsEvents/Newsroom/FactSheets/ucm514939.htm. You also state that the Agency disregarded report findings that Reformulated OxyContin can be crushed to a fine powder using a coffee grinder (Petition at 9, 10). FDA has explained that, with any abuse-deterrent formulation, abuse-deterrent properties "can be defeated with sufficient time, equipment and expertise," and "[t]hese limitations may be impossible to completely overcome as these products must release the opioids they contain to have their intended therapeutic effects" (79 FR 56810, 8611, September 23, 2014).

[75] Nor is it relevant that Reformulated Opana "was stronger and less susceptible to manipulation" than Reformulated OxyContin (Petition at 15), as neither formulation has approved abuse-deterrent labeling claims with respect to the oral route of abuse.

[76] You claim that the CDER Exclusivity Board's findings "indicate that OTR1018 does not meet the FDA standards of 'adequate and well controlled' per 21 CFR 314 and is insufficient to support [Reformulated OxyContin's] abuse deterrent labeling" (Petition at 17-18). Nothing in the CDER Exclusivity Board memorandum to which you refer suggests that the study was insufficient to support abuse-deterrent labeling.

'powered' oxycodone HCl" (Petition at 17). Although this statement is technically correct, it is misleading because the study also found a statistically significant difference in Drug Liking for insufflation of ground Reformulated OxyContin when compared to insufflation of Original OxyContin. In study OTR1018, insufflation of ground Reformulated OxyContin was compared to insufflation of two positive controls: powdered oxycodone HCl API and ground Original OxyContin.[77] Insufflation of finely ground Reformulated OxyContin resulted in reduction in E_{max} of Drug Liking of 8.9 millimeters (mm) when compared to oxycodone HCl API powder and 13.6 mm when compared to ground Original OyxContin.[78] We believe that Original OxyContin is a more relevant positive control than powered oxycodone HCl, and the reduction in E_{max} of Drug Liking of 13.6 mm when comparing insufflation of ground Reformulated OxyContin to insufflation of ground Original OxyContin was statistically significant and considered to be potentially clinically relevant.

Data supporting the abuse-deterrent claim with respect to insufflation were not limited to Drug Liking. With use of the bipolar Take Drug Again VAS, there was a reduction of 25.6 mm (from 89.6 mm to 64.0 mm) following insufflation of finely crushed Reformulated OxyContin compared to finely crushed Original OxyContin.[79] This reduction in Take Drug Again VAS was statistically significant and considered to be very likely clinically relevant. Descriptive statistics showed that approximately 37% of subjects (10 out of 27) and 55.6% of subjects (15 out of 27) in the study had at least a 30% reduction in drug liking E_{max} following intranasal administration of finely and coarsely crushed Reformulated OxyContin tablets respectively, relative to finely crushed Original OxyContin.[80] Accordingly, data from OTR1018 suppport that Reformulated OyxContin's can be expected to deter abuse by insufflation.

In sum, the Agency appropriately relied upon study OTR1018 to support Reformulated OxyContin's abuse-deterrent labeling with respect to intranasal abuse.[81]

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[77] See DRUG ABUSE AND DEPENDENCE, *Abuse*, Reformulated OxyContin labeling, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/022272s034lbl.pdf.

[78] Id.

[79] Id.

[80] Id. You also state that study OTR1018 "used only pharmacodynamic data to approve abuse deterrent labeling for OxyContin," and the "data did not reach the required 'meaningful statistical analysis' cited in the FDA's guidance" (Supplement at 3). The Evaluation and Labeling Guidance's section on statistical analysis states that "[t]he primary analysis of abuse-deterrent effects should be based on the comparison of means between crushed, chewed, or otherwise modified *T* [potentially abuse-deterrent product] and *C* [formulation of the drug without abuse-deterrent properties] with an abuse deterrence margin on drug liking VAS." Evaluation and Labeling Guidance at 14. Additionally, the final guidance states that "[i]n addition to the primary analysis, an analysis should be performed of the percent reduction for the potentially abuse-deterrent product T to C from each individual study subject for drug liking VAS on a bipolar scale from 0 to 100." Evaluation and Labeling Guidance at 15. The statistical analysis for study OTR1018 is consistent with the guidance. See DRUG ABUSE AND DEPENDENCE, *Abuse*, Reformulated OxyContin labeling, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/022272s034lbl.pdf.

[81] You claim that Reformulated OxyContin's abuse-deterrent labeling claims were approved "based upon one and only one liking study, OTR1018" (Supplement at 2),which is incorrect. As stated above in Section I.B., Refomulated OxyContin's abuse-deterrent labeling claims were supported by data from in vitro, PK, clinical abuse potential, and epidemiologic studies.

4. Claim That Postmarketing Epidemiology Data Fail to Establish That Reformulated OxyContin Has Meaningful Abuse Deterrence

You state that "Purdue's epidemiology studies submitted to the FDA did not support an abuse-deterrent claim" and that "after 5 years post-approval, there exists a vast amount of data showing that [Reformulated OxyContin] has no abuse deterrent effect" (Petition at 18). In support of your claims, you cite a report by the Centers for Disease Control and Prevention (CDC) and an FDA News Release, neither of which address postmarketing data for Reformulated OxyContin.[82] You also refer to statements made by Dr. Judy Staffa, the Associate Director of Public Health Initiatives within CDER's Office of Surveillance and Epidemiology, at the September 11, 2015 joint meeting of the AADPAC and the DSaRM Advisory Committee (Petition at 18), in which she cautioned that the Agency has "not yet seen data that suggest that [Reformulated OxyContin] has actually made a meaningful reduction in abuse," claiming that her statements "highlighted the lack of any meaningful reduction in abuse" (Petition at 18). Dr. Staffa did not opine that postmarketing data showed that Reformulated OxyContin's abuse-deterrent properties failed to result in a reduction in abuse, only that data affirmatively establishing such a reduction have not yet been seen.[83]

It is notable that during the review of Reformulated OxyContin's abuse-deterrent labeling, CDER found the postmarketing data at the time "suggest, but do not confirm that the reformulation of OxyContin has resulted in a decline in non-oral abuse."[84] Indeed, Purdue has yet to complete the postmarketing studies that it is required to conduct to assess the impact of the product's properties on abuse in the real world setting.[85] The Agency expects to review and evaluate the reports of those studies, once they have been completed and submitted, before reaching any conclusion about the impact of the product's abuse-deterrent features.

As noted in section II.C, the data sources available for postmarketing studies, primarily non-random samples of interviews of individuals admitted to centers for treatment of substance abuse disorders and addictions and calls to poison control centers, have limitations. FDA hosted a public meeting in July 2017 to discuss the challenges posed by postmarket assessments, as well as opportunities for collecting and/or linking additional data to improve national surveillance and

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[82] CDC, *Morbidity and Mortality Weekly Report, QuickStats: Rates of Deaths from Drug Poisoning Involving Opioid Analgesics*, 64(01); 32 (January 16, 2015); FDA News Release, *FDA moves quickly to approve easy-to-use nasal spray to treat opioid overdose* (November 18, 2015). The CDC report focuses on the total deaths in the United States attributed to drug poisoning, including deaths involving opioid analgesics and the drug poisoning death rates, including the rate for drug poisoning deaths involving opioid analgesics from 1999 to 2006. The CDC report does not parse out data for abuse-deterrent opioids or for Reformulated OxyContin. The FDA News Release announced the approval of Narcan Nasal Spray and did not include any information on Reformulated OxyContin or its postmarketing requirements. The FDA News Release cites to a 2013 CDC report that includes data on prescription overdose deaths between 1999 and 2014 but does not include data specific to abuse-deterrent opioids or Reformulated OxyContin.

[83] See transcript for the September 11, 2015 Joint Meeting AADPAC and DSaRM Advisory Committee at 305-306.

[84] Memorandum from Gerald Dal Pan to Douglas Throckmorton (April 12, 2013, Ref. ID: 3292602) at 7, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/022272Orig1s014OtherR.pdf.

[85] You can access information on an applicant's postmarketing requirements at Postmarket Requirements and Commitments, available at http://www.accessdata.fda.gov/scripts/cder/pmc/index.cfm.

research capabilities in this area.[86] At present, however, the availability of postmarketing data regarding abuse deterrence, and methods to collect it, continue to be further developed and refined.

For these reasons, we do not agree with PMRS's arguments regarding currently available postmarketing data for Reformulated OxyContin.

In sum, we do not agree that the studies supporting the approval of abuse-deterrent labeling for Reformulated OxyContin were flawed. Accordingly, we deny your requests to revise the labeling for Reformulated OxyContin to remove the abuse-deterrent claims, to revoke the three-year grant of exclusivity to Purdue for Reformulated OxyContin, or to "restore" Original OxyContin to marketing. We also decline to find that Reformulated OxyContin is misbranded.

III. CONCLUSION

For the reasons described above, your requests are denied.

Sincerely,

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

[86] See Data and Methods for Evaluating the Impact of Opioid Formulations With Properties Designed To Deter Abuse in the Postmarket Setting: A Scientific Discussion of Present and Future Capabilities, Docket No. FDA-2017-N-2903 (82 FR 27271, June 14, 2017).