PHARMACEUTICAL MANUFACTURING RESEARCH SERVICES, INC.

February 19, 2016

Via Electronic Submission

Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061

Rockville, MD 20852

CITIZEN PETITION

The undersigned, on behalf of Pharmaceutical Manufacturing Research Services, Inc. ("PMRS"), submits this petition pursuant to 21 C.F.R. §§ 10.20 and 10.30 to the U.S. Food and Drug Administration ("FDA") requesting that the Commissioner of the FDA (i) uniformly apply its standards for permitting a drug to be labeled as abuse deterrent by (a) requiring pre-marketing scientific proof of manipulation and extraction studies for abuse deterrent formulations in both *small* and *large* volume extraction and (b) requiring post-marketing empirical proof in the field of abuse deterrence before allowing a drug to be labeled abuse deterrent, and (ii) as a consequence thereof, require all drug products currently labeled abuse deterrent meet these standards or have its abuse deterrent labeling withdrawn.

There is currently an opioid epidemic in the United States. The FDA has recently expressed its deep concern "about the growing epidemic of opioid abuse, addiction, and overdose — an epidemic directly related to the increasingly widespread misuse of powerful opioid pain medications." *A Proactive Response to Prescription Opioid Abuse*, by Robert M. Califf, M.D., Janet Woodcock, M.D., and Stephen Ostroff, M.D, New England Journal of Medicine (2016) (the "FDA Report").[1] It has also acknowledged that new steps need to be taken to cope with the crisis of opioid misuse.

> As FDA leaders and as physicians, we believe that these efforts must be founded on two complementary principles: that the United States must deal aggressively with opioid misuse and addiction, and at the same time, that it must protect the well-being of people experiencing the devastating effects of acute or chronic pain. It is a difficult balancing act, but we believe that the continuing escalation of the negative consequences of opioid use compels us to comprehensively review our portfolio of activities, reassess our strategy,

[1] *A Proactive Response to Prescription Opioid Abuse*, by Robert M. Califf, M.D., Janet Woodcock, M.D., and Stephen Ostroff, M.D, New England Journal of Medicine (2016), p. 1.

> and take aggressive actions when there is good reason to believe that doing so will make a positive difference.[2]

Furthermore, the FDA Report highlights the need for more and better abuse deterrent drugs as well as strategies for encouraging development of these drugs as paramount to ending the widespread misuse of opiates.[3] The inconsistent application of the current standards has led to the approval of drug products labeled as having abuse deterrent properties, but which result in no abuse deterrence. Rather than producing a decrease in opioid sales or opioid related deaths, sales of so called "abuse deterrent" drug products have increased as have the number of deaths associated therewith.

It is respectfully submitted that as part of this aggressive action, the FDA must revisit how it applies its standards to determine whether a drug can be properly labeled as having abuse deterrent properties. Current FDA standards are actually delaying entry of true abuse deterrent drugs into the market by requiring expensive pre-market subjective "liking" tests. These "liking" tests lack scientific rigor and fail to uniformly require that abuse deterrent formulations address known ways to obtain street quantities of opioids in small batch production.

More effective action is desperately needed. This means that to obtain abuse deterrent labeling a drug must be objectively determined to be abuse deterrent by both in-vitro chemical pre-market testing and by post-market epidemiological studies. This is in keeping with the FDA's announced strategy to put more emphasis on post-marketing opioid misuse and abuse data.

> The FDA will revise postmarketing requirements, expanding the requirements for drug companies to generate postmarketing data on long-term impact of ER/LA opioid use to provide better evidence on the serious risks of misuse and abuse associated with long-term opioid use, predictors of opioid addiction, and other important issues.[4]

Five FDA approved drug products presently have approval for abuse deterrent formulation ("ADF") labeling. The failings of the FDA's current standards, as applied, can be demonstrated by highlighting one of them, namely OxyContin®, as a case study. OxyContin® is an extended release tablet containing high amounts (e.g., up to 80 mg) of oxycodone hydrochloride and is purported to have meaningful abuse deterrent properties. Purdue Pharma ("Purdue") is the holder of NDA 022272 for OxyContin® tablets which are currently approved with abuse deterrent labeling (herein, "Reformulated OxyContin®", "OCR" or "ORF"). The FDA's inconsistent application of the current standards, including its failure to require uniform testing of opioid formulations, has led to the improper labeling of Reformulated OxyContin® as abuse deterrent.

[2] Id.
[3] Id. p. 2.
[4] Id.

202 Precision Road • Horsham, PA 19044 • Phone (267) 960-3300

In April 2010, Purdue received approval of NDA 022272 for Reformulated OxyContin®; at that time, Purdue was denied abuse deterrent labeling. As a condition for approval of NDA 022272, the FDA issued a post-marketing requirement to Purdue to conduct epidemiological studies to assess whether the changes made to the Reformulated OxyContin® formulation resulted in a decrease in misuse, abuse, addiction, overdose and death.

In April 2013, the FDA approved abuse deterrent labeling for Reformulated OxyContin® based on a "liking" study (OTR1018) that purported to show that Reformulated OxyContin® has meaningful abuse deterrent properties. The "liking" study relied upon by the FDA in this determination is not only subjective, it does not meet the required standard of adequate, well-controlled, robust, rugged and scientifically rigorous testing spelled out in the recently issued Guidance for Industry (the "Guidance") requirements that "studies designed to evaluate the abuse-deterrent characteristics of an opioid formulation should be scientifically rigorous" and that have "data analyses to permit a meaningful statistical analysis."[5] Importantly, the approval of the abuse deterrent labeling was not based on epidemiological studies as required in the approval of NDA 022272. Nonetheless, shortly thereafter, the FDA removed NDA 020553 for original OxyContin® ("OC") from the Orange Book for safety reasons.

In April 2013, the FDA granted Purdue a three (3) year exclusivity period for Reformulated OxyContin® based ultimately on the same "liking" study (OTR1018) that purported to show that Reformulated OxyContin® has meaningful abuse deterrent properties.

Post-marketing epidemiological studies have consistently shown that Reformulated OxyContin® does not result in meaningful reductions in misuse, abuse, addiction, overdose or death. Despite the introduction of Reformulated OxyContin® in 2010 and the abuse deterrent labeling in 2013, the misuse, abuse, addiction, overdose and death caused by, or associated with, Reformulated OxyContin® abuse continues to rise.

A. ACTION REQUESTED

PMRS requests that the 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;[6]

(ii) Remove Category 3 human abuse-deterrent (liking) studies from the 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 potential abuse deterrent properties do

[5] "Abuse-Deterrent Opioids Evaluation and Labeling Guidance for Industry" published April 2015, p. 4.
[6] The current, but different, standards would apply to drugs seeking ADF labeling solely on the basis of aversion.

202 Precision Road • Horsham, PA 19044 • Phone (267) 960-3300

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 below, because the current Reformulated OxyContin® cannot meet these standards, the FDA should take immediate actions for the reasons stated in the recent FDA Report 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 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 upon 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. Post-marketing epidemiology clearly establishes that Reformulated OxyContin® has no meaningful abuse deterrent effects.

PMRS respectfully submits that undertaking such actions will help to accomplish the goals set forth in the FDA Report, including balancing the individual need and societal risk, meeting the need for timely action, reviewing abuse deterrent labeling and prioritizing the required FDA standards for abuse deterrent formulations. Such actions will send the necessary message to the industry that scientific rigor is required in the development of effective abuse deterrent features before permitting an ADF label on an opioid drug product. PMRS notes that state legislators are already introducing legislation to relax prescription standards for ADF drug products in reliance upon the FDA's designation, which could add fuel to the current raging fire of opioid addiction.

Highlighting the need for demonstrable, scientific proof of abuse deterrence is a challenge that industry can, and must, meet to develop real abuse deterrent drug products that are shown to

202 Precision Road • Horsham, PA 19044 • Phone (267) 960-3300

work, both in the laboratory and in clinical practice. The establishment of clear and objective standards, as requested, would speed development of new abuse deterrent drug products and avoid the current expensive, wasteful, and delaying pre-market "liking" studies that do not contribute any meaningful proof of abuse deterrence.

B. STATEMENT OF GROUNDS

I. FDA'S GUIDANCE FOR INDUSTRY ON ABUSE DETERRENT FORMULATIONS

The FDA recognizes the need for new abuse deterrent opioid formulations to combat the rising abuse of opioids. In April 2015, the FDA published the latest version of its guidance titled "Abuse-Deterrent Opioids Evaluation and Labeling Guidance for Industry." The Guidance represents the FDA's current thinking on what studies are needed to demonstrate that formulations are abuse deterrent.

The Guidance defines abuse deterrent properties as "those properties shown to **meaningfully** [emphasis added] deter abuse, even if they do not fully prevent abuse." "It means, rather, that the risk of abuse is lower than it would be without such properties."[7]

The Guidance states that "the science of abuse deterrence is relatively new" and "rapidly evolving." "The FDA intends to take a flexible, adaptive approach to the evaluation and labeling of potentially abuse-deterrent products."[8] "This flexibility is intended to permit a sponsor to tailor the development program to suit the abuse-deterrent characteristics of their product and the routes of abuse for that product."[9]

"No absolute magnitude of effect can be set for establishing abuse-deterrent characteristics. As a result, FDA intends to consider the *totality of the evidence* when reviewing the results of studies evaluating the abuse-deterrent properties of a product."[10]

The Guidance requires that "[f]irst and foremost, any studies designed to evaluate the abuse-deterrent characteristics of an opioid formulation should be **scientifically rigorous**" [emphasis added] [e.g., well-defined; reliable] and provide "**data analyses to permit a meaningful statistical analysis.**"[11] [emphasis added]. The Guidance does not eliminate or waive the statutory requirement that studies supporting FDA approvals be robust, rugged and scientifically rigorous. *See* 21 CFR 314.126 "Adequate and well-controlled studies."

21 CFR 314.126 titled "Adequate and well-controlled studies" sets forth the requirements for clinical investigations to distinguish the effect of a drug from other influences. "An adequate and well-controlled study has the following characteristics:

---

7 Guidance., p. 2.
8 Id.
9 Id. p. 5.
10 Id. p. 2.
11 Id. p. 4.

202 Precision Road • Horsham, PA 19044 • Phone (267) 960-3300

> (b)(2) The study uses a design that permits a valid comparison with a control to provide a quantitative assessment of drug effect;
>
> (b)(6) The methods of assessment of subjects' response are well-defined and reliable. The protocol for the study and the report of results should explain the variables measured, the methods of observation, and criteria used to assess response; and
>
> (e) Uncontrolled studies or partially controlled studies are not acceptable as the sole basis for the approval of claims of effectiveness.

The Guidance sets forth the four categories of testing[12]:

Category 1 – Laboratory-based in vitro manipulation and extraction studies.

Category 2 – Pharmacokinetic studies comparing in vivo properties of intact vs. manipulated formulations by different administration routes.

Category 3 – Clinical abuse potential studies, or "liking" studies, testing the subjective effect of manipulated drug product vs. API on drug-experienced, recreational user populations.

The Guidance recognizes that "liking" studies are subjective and lack rigor. "The primary method for evaluating **the subjective effects** of drugs should be through the use of standardized instruments."[13] [emphasis added]. The 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**."[14] [emphasis added].

Category 4 – Post-market studies. "The goal of post-market studies, Category 4, is to determine whether the marketing of a product with abuse-deterrent properties results in meaningful reductions in abuse."[15] The FDA recognizes the overarching importance of post-market studies for evaluating an abuse deterrent effect. "Premarket studies are intended to demonstrate properties that are predictive of a meaningful abuse-deterrent effect."[16] Whereas, **post-market studies "determine whether the marketing of a product with abuse-deterrent properties results in a meaningful reduction**."[17] [emphasis added].

The FDA anticipates amending a drug product's abuse deterrent labeling based on the results of post-market studies. "If these post-market data fail to confirm that the abuse-deterrent properties result in a reduction in abuse, or demonstrate a shift in routes of abuse that represent a greater

[12] Id. p. 5.
[13] Id. p. 12.
[14] Id. p. 5.
[15] Id. p. 17.
[16] Id. p. 22.
[17] Id. p. 17.

202 Precision Road • Horsham, PA 19044 • Phone (267) 960-3300

risk (e.g., a shift from oral and nasal abuse to intravenous abuse), **FDA may determine that labeling revisions are needed.**"[18] [emphasis added].

Further, the FDA understands that "abusers may adapt to abuse-deterrent technologies and discover methods to defeat them. If and when abusers can overcome a technology such that it no longer has a meaningful effect in deterring abuse, **FDA may require labeling revisions.**"[19] [emphasis added].

II. THE CASE STUDY OF OXYCONTIN® (ORIGINAL AND REFORMULATED)

In December 1995, the FDA approved Purdue's original formulation of OxyContin®, an extended release formulation containing between 10-40 mg oxycodone.[20] By 2000, additional strengths of 80 and 160 mg were added. Upon entering the market, the product was manipulated for abuse to defeat its extended release properties. For example, original OxyContin® could be chewed before swallowing, or ground before snorting, and subsequently "dose dump" the majority of the active for immediate release. The rapid release increased the risk of serious adverse events, including overdose and death.

In November 2007, Purdue submitted NDA 022272 for Reformulated OxyContin®, including in vitro data[21] purported to show abuse deterrence of the tablets.[22] Purdue requested approval of OCR and approval of abuse deterrent labeling. The abuse deterrent properties of OCR were attributed, in part, to the inclusion of a polyethylene oxide polymer (PEO) in the formulation. The specific PEO polymer used is thought to make the drug product more resistant to crushing, chewing and dose-dumping. The PEO polymer is also thought to form a viscous gel when exposed to water and the physical properties of the polymer are thought to produce tablets with increased resistance to crushing.[23]

In April 2010, the FDA approved OCR under a 505(B)(2) application showing bioequivalence to the reference listed drug. OCR did not receive abuse deterrent labeling. The FDA required additional studies, including post-market epidemiological studies, to help determine the potential abuse deterrent effect of OCR. In August 2010, Purdue stopped sales of its original OxyContin®.

---

[18] Id. p. 22.

[19] Id. p. 23.

[20] The approval of an extended release opioid drug product is, in itself, questionable. Patient compliance with narcotic pain medication is not an issue. The goal should be pain relief using minimum effective dosing. The primary indication for an extended release opioid drug product should be to prevent overnight breakthrough pain.

[21] The in vitro data from the NDA is not available. However, the in vitro data is summarized in various FDA documents related to OCR's approval.

[22] In 2007, Purdue and three of its executives were fined $634.5 million for misleading the regulators and the public about OC's risk of addiction. The evidence included numerous people who said their lives were changed forever by addiction to OC, a long-acting form of the painkiller oxycodone. Designed to be swallowed whole and digested over 12 hours, the pills can produce a heroin-like high if crushed and then swallowed, snorted or injected.

[23] Chemistry Review, 2008, Craig M. Bertha, Ph.D., ONDQQ/Division I/Branch 2, p. 12.

202 Precision Road • Horsham, PA 19044 • Phone (267) 960-3300

In September 2012, Purdue petitioned the FDA for abuse deterrent labeling for OCR. Purdue's Supplemental application (S014) included additional studies related to the abuse deterrent properties of OCR.[24]

In April 2013, the FDA approved the Supplement application (S014) for OCR abuse deterrent labeling. The FDA summarized the abuse deterrent evidence as follows: "The physiochemical differences between [OCR] and OxyContin ***appear*** to make OCR more difficult to use by the intravenous and intranasal routes and, to a lesser extent, to overcome the controlled-release properties by the oral route."[25] [emphasis added]. The FDA cited five (5) studies as being submitted to support the approval of abuse deterrent labeling. The five studies are summarized below.

In April 2013, the FDA removed NDA 020553 for the original OxyContin® from the Orange Book.[26] The withdrawal of the NDA from sale was for safety reasons.[27]

A. Summary of Purdue's Five (5) Abuse Deterrent Studies Supporting Approval of Reformulated OxyContin® and Epidemiological Reports

The five studies in the Approval Package for Reformulated OxyContin® include: OTR1016, OTR1018, OTR1019, OTR1021 and OTR1022.

OTR1016 - This was a study of the effect of chewed and crushed OCR. The study finds that "upon vigorous chewing, OCR and OC are bioequivalent."[28]

The FDA has stated that "the vast majority of deaths associated with OC were related to oral consumption."[29] Oral consumption is the main route of abuse in the form of "dose dumping" or chewing/grinding/swallowing, as opposed to intranasal or intravenous administration. This study clearly indicates that OCR "dose dumps" when chewed and swallowed, same as OC. "Overall, these studies indicate that the controlled release properties of the OCR can be overcome when chewed vigorously and swallowed, but the controlled-release properties of OCR were slightly less susceptible to compromise than OC when chewed normally."[30]

The Controlled Substance Staff's review conclusion states, "Assuming that across studies there is a similar correlation of oxycodone plasma concentrations to drug liking scores on the Drug Liking VAS, it is predicted that vigorous chewing followed by ingestion of either an ORF 40 mg tablet, a crushed (mortar and pestle) ORF 40 mg tablet, or a pre-softened ORF 40 mg tablet will

[24] The data from the Supplemental submission is not available. However, the data is summarized in various FDA document related to abuse deterrent labeling of OCR.
[25] FDA Reference ID: 3258740, p. 3.
[26] It is noted that the removal of the NDA for original OxyContin® from the Orange Book has prevented generic companies from selling original extended release OxyContin®.
[27] *See* Docket No FDA 2012-p.-0895, p. 4
[28] FDA Reference ID: 3258740, p. 8.
[29] Id. p. 5-6.
[30] Id. p. 6.

202 Precision Road • Horsham, PA 19044 • Phone (267) 960-3300

produce significant levels of drug liking indicative of positive subjective reinforcing effects."[31] The CSS predicted that ORF would fail the abuse deterrent "liking" studies, which it did.

OTR1018 - This was a study of the effect of "coarsely" and "finely" crushed OCR (razor blade and coffee mill, respectively) versus "finely" crushed OC (mortar and pestle) and oxycodone API powder via insufflation. The study finds that "OCR has lower intranasal abuse potential than OC."[32]

The FDA has stated, however, that OCR "can still be crushed to a fine powder using a coffee grinder."[33] OTR1018 is further discussed below.

OTR1019 - This was a study that simply informed abusers about the drug product and recorded abuser's comments. This study was described by the FDA reviewer as "poorly designed."[34]

OTR1021 - This was a study of the pharmacokinetics of "coarsely" and "finely" crushed OCR (razor blade and coffee mill, respectively) versus "finely" crushed OC (mortar and pestle). The study is described as "less informative than OTR1018" and "adds little to the overall conclusion regarding this formulation." [35] This study suffers from the same deficiencies as OTR1018, as discussed below.

OTR1022 - This was a study to assess tolerability of intranasal administration of OCR. The study finds that "the effects of OCR and OC's non-active components are not expected to be a deterrent to intranasal abuse." [36]

Epidemiology - Regarding epidemiology, the FDA summarized that "Purdue has conducted six epidemiology studies to fulfill the post-marketing requirement and five additional epidemiology studies. The Division of Epidemiology (DEPI) reviewed an interim report on these studies . . . . the findings were not mature enough to support an abuse-deterrent claim."[37] The OSE Division of Epidemiology II memorandum to Dr. Throckmorton by Dr. Gerald Dal Pan, MD, MHS on the "impact of [OCR] on OxyContin® abuse," stated the following: "[t]aken as a whole, these investigations suggest, but do not confirm, that OCR has resulted in a decline in non-oral abuse. Furthermore, **the data available at this time cannot support a robust conclusion that the reformulation of OxyContin® is responsible for an overall decline in OxyContin® abuse.**"[38] [emphasis added].

With the FDA's dismissal of Purdue's epidemiology studies, the overall conclusion regarding whether there is robust and meaningful evidence to conclude that OCR is abuse-deterrent was

[31] Id. p. 7.
[32] Id. p. 8-9.
[33] Id.
[34] Id. p. 10.
[35] Id. p. 11.
[36] Id.
[37] Id.
[38] FDA Reference ID: 3292602, p. 1.

202 Precision Road • Horsham, PA 19044 • Phone (267) 960-3300

provided by the DAAAP Director on February 6, 2013. *The overall conclusion is OCR provides two benefits, namely(i) reduced ability to crush and abuse intranasally, and (ii) reduced ability to syringe and abuse intravenously.*

> "The physicochemical differences between OCR and OxyContin® appear to make OCR more difficult to use by the intravenous and intranasal routes and, to a lesser extent, to overcome the controlled-release properties by the oral route."[39] "These features also render the product almost impossible to dissolve, syringe, and inject."[40]
>
> "The Controlled Substance Staff reviewed these studies and concluded that the new formulation had abuse-deterrent properties and had demonstrated an advantage over the previous OxyContin formulation by showing that the tablets are considerably more difficult to chew or crush and more difficult to convert to an aqueous solution suitable for intravenous injection."[41]

B. The In Vitro Data Relied Upon by the FDA to Approve Abuse Deterrent Labeling Is Incomplete

The FDA originally approved Reformulated OxyContin® in April 2010 but did not approve abuse deterrent labeling at that time. In April 2013, the FDA approved abuse deterrent labeling for Reformulated OxyContin® on the basis of two benefits, namely (i) a reduced ability to crush and abuse intranasally, and (ii) a reduced ability to syringe and abuse intravenously.

This finding ignores the Controlled Substance Staff report that "ORF[s] can still be crushed to a fine powder using a coffee grinder."[42] Regarding intranasal abuse, the FDA relied solely on the subjective, inadequate and not well-controlled "liking" study OTR1018 ("OTR1018 was essential to approval" and "no other data exists to support approval of this supplement").[43] As detailed below, OTR1018 cannot support a meaningful abuse deterrent effect.

Regarding intravenous abuse, the FDA relied on the well-known behavior of Reformulated OxyContin® excipients to form a hydrogel when exposed to a large volume aqueous solution and/or when agitated. The FDA failed to require actual testing of small volume extraction. The FDA knew, or should have known, that such testing would confirm its susceptibility to common techniques that would isolate oxycodone from Reformulated OxyContin® for abuse or distribution on the street.

Finally, the FDA failed to recognize Reformulated OxyContin®'s negligible effect on crushing and therefore dose dumping - the primary abuse route.

C. Oxycodone Can Be Extracted from Reformulated OxyContin® by Small Volume Extraction

[39] FDA Reference ID: 3258740, p. 3.
[40] FDA Reference ID: 3293880, p. 2.
[41] FDA Reference ID: 3258740, p. 4.
[42] Id. p. 5.
[43] FDA Reference ID: 3712567, p. 4-5.

202 Precision Road • Horsham, PA 19044 • Phone (267) 960-3300

In the Guidance, the FDA recognizes that abusers may adapt to abuse deterrent technologies and discover methods to defeat them. Based on the epidemiology data provided herein, abusers appear to have readily adapted to OCR's formulation because sales of OCR and deaths associated with OCR have continued to rise unabated.

Abusers have adapted, in part, because the extraction of oxycodone from OCR is exceedingly easy. Oxycodone can be extracted in high yields and high purity from OCR by [redacted] the extract can be intravenously injected immediately. [redacted] highly pure API can be recovered.[44]

Prior to OCR approval, the FDA was aware of the potential for abuse by small volume extraction. The FDA denied abuse deterrent labeling for a similarly formulated extended release opioid,[45] namely Endo Pharmaceuticals Opana® or "OPR" based, in part, on the fact that the oxymorphone can be extracted from OPR formulations in high yields and high purity via small volume extraction. (Discussed further below). Without explanation, the FDA failed to test OCR for abuse by small volume extraction.

The abuse deterrent properties of Reformulated OxyContin® appear to be associated with the inclusion of a high molecular weight (HMW) PEO within the formulation. It is known that HMW PEO can form a hydrogel when exposed to a large volume of aqueous solution and/or when agitated (See, e.g., U.S. Patent No. 7,776,314). The hydrogel can discourage drawing the solution into a syringe for intravenous injection. Yet, oxycodone can be recovered from OCR without the PEO forming a hydrogel when the formulation is [redacted] 80 mg OCR tablet can yield a clear solution that contains a high yield ([redacted]) of oxycodone. The extracted product can be drawn into a syringe for intravenous injection.

Oxycodone can also be recovered from OCR [redacted] The extracted product can be re-dissolved for intravenous administration or insufflated.

The FDA's finding that "it is more difficult to prepare a solution for intravenous injection using OCR than original OC as a result of the inclusion of the excipient polyethylene oxide" is wrong.[46] It is, in fact, easier to abuse OCR because of the inclusion of PEO in OCR tablets. The

[44] Each of these processes takes approximately 30 minutes to complete and can be readily demonstrated through a video.
[45] Both reformulated OxyContin® and Opana® are licensed under common patents.
[46] Docket FDA 2012-p.-0895, p. 5-6.

202 Precision Road • Horsham, PA 19044 • Phone (267) 960-3300

oxycodone can be extracted to a higher purity from OCR because OCR does not contain the additional excipients found in original OC.[47]

D. No Small Volume Extraction Testing Performed on Reformulated OxyContin®

In relation to Reformulated OxyContin® the FDA understood the role, or lack thereof, polyethylene oxide (PEO) plays in a formulation. The following statements were made regarding the approval of Reformulated OxyContin®:

- "[REDACTED] percent of oxycodone can be extracted from ground OCR using water compared to [REDACTED] in OC; [REDACTED] of oxycodone can be extracted from intact OCR."[48]

- This finding is relevant because it establishes that water extraction of oxycodone from manipulated OCR was investigated.

- "It is more difficult to prepare a solution for intravenous injection using OCR than original OC as a result of the inclusion of the excipient polyethylene oxide."[49]

Dr. Throckmorton, Deputy Director, CDER states that "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."[50] PEO does form a hydrogel in an aqueous solution – but only when the solution contains a large volume of water and/or is agitated. The basic understanding that PEO can form a hydrogel was known in 2003 and forms one of the bases for U.S. Patent No. 7,776,314 (listed in the Orange Book for OCR and having a priority claim to 2003).[51] The '314 patent claims a formulation containing a viscosity-increasing agent (e.g., PEO) that forms a hydrogel when combined (e.g., shaken) with 10 mL of water such that "remains visually distinguishable" (e.g., has strands) when passed through a needle into a second aqueous solution. *See* Claim 1 of the '314 Patent.

Yet, the FDA does not address the extraction of oxycodone from OCR using [redacted] small volume extraction. The FDA does, however, discuss small volume extraction of OC. In a memorandum by Dr. Throckmorton[52], Dr. Throckmorton summarized the syringeability testing of OCR as follows: "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 concentration. **By**

[47] FDA Reference ID: 3258740, p. 5-6.
[48] Id.
[49] Id.
[50] FDA Reference ID: 329414, p. 9.
[51] Purdue cites to the hydrogelling properties to show generic tablets infringe the '314 patent. *See* In re: OxyContin® Antitrust Litigation, Purdue v. Teva, 994 F. Supp. 2d 367 (S. D. NY 2014). The FDA's findings on syringability are contradictory to Purdue's construction of the '314 claims requiring syringability.
[52] Dr. Throckmorton is the Asst. Director of CDER.

202 Precision Road • Horsham, PA 19044 • Phone (267) 960-3300

contrast, low volume, highly concentrated aqueous solutions of oxycodone for intravenous use can be readily obtained from OC tablets."[53] [emphasis added] There is no acknowledgement of similar testing of low volume aqueous solutions of oxycodone for intravenous use from OCR tablets.

E. Reformulated OxyContin® "Dose Dumps" Similar to Original OxyContin®

Reformulated OxyContin® provides no significant abuse deterrence to the primary known route of abuse for OC. The FDA Guideline states that "the evaluation of an abuse-deterrent formulation should take into consideration the known routes of abuse."[54] In evaluating OCR, the FDA stated that the vast majority of abuse with OC is by oral consumption (i.e., chewing and swallowing). The two benefits of OCR cited by the FDA for approval, i.e., a reduced ability to crush and abuse intranasally, and a reduced ability to syringe and abuse intravenously, are of lesser concern than a reduction in dose dumping. Yet, OCR does not reduce dose dumping. OCR "dose dumps" similar to OC. "The *in vitro* data, together with the pharmacokinetic data, show that while OCR is more difficult to crush that OC, vigorous chewing is sufficient to defeat the extended-release features of **OCR to a similar degree as that seen with OC**."[55] [emphasis added] The Controlled Substance Staff's review conclusions for OTR1016 concluded "[u]pon chewing vigorously, OFR and OC products are bioequivalent with respect to oxycodone Cmax and AUC."

The fact that OCR dose dumps is not surprising. Another reason the FDA denied abuse deterrent labeling to OPR was because OPR dose dumps. Comparative testing of the two formulations (OPR vs. OCR) show that OPR is stronger and less susceptible to manipulation and abuse than OCR. This is primarily due to the excipients and preparation methods.

What is surprising is the FDA knew OCR dose dumped with vigorous chewing (e.g., via Purdue's OTR1016 study) but approved abuse deterrent labeling anyway.[56]

III. THE FDA HAS APPLIED ITS STANDARDS INCONSISTENTLY

A. The FDA Denied Opana® Abuse Deterrent Labeling Based on Small Volume Extraction

[53] FDA Reference ID: 3294145, p. 13.
[54] Guidance p. 4.
[55] FDA Reference ID: 3294145, p. 9.
[56] FDA, p.-095 docket, FN 14. Other products such as Endo's Opana ("OP") have been denied abuse deterrent labeling for the same reason by the FDA:

> "Although it is possible that OPR's crush-resistance may deter some misuse, such as improper crushing for administration with food or through a feeding tube, OPR remains susceptible to other types of unintentional misuse, such as causing the product to "dose dump" by cutting or chewing then swallowing. Inclusion of language regarding reduced crushability in the labeling could be misleading and result in health care practitioners or patents thinking that OPR is safer than OP, and that it is safe to chew OPR; or that it is safe to give OPR to vulnerable populations."

202 Precision Road • Horsham, PA 19044 • Phone (267) 960-3300

In June 2006, the FDA approved Endo's original formulation of Opana® ("OP") which is an extended release formulation containing oxymorphone. Similar to OC, OP was manipulated for abuse to defeat its extended-release properties. For example, OP could be chewed before swallowing and "dose dump" the majority of the active for immediate release. Endo subsequently developed and sought approval for an abuse deterrent form of oxymorphone (OPR).

In December 2011, the FDA approved OPR under a 505(B)(2) application showing bioequivalence to the reference listed drug. OPR did not get approval for abuse deterrent labeling upon initial approval.

In August 2012, the FDA denied Endo's request for abuse deterrent labeling for OPR. Despite the FDA admitting that OPR had some abuse deterrent properties, the FDA relied, in part, on the fact that OPR can (i) "dose dump" and can (ii) more easily be prepared for injection than OP.

> "While there is an increased ability of OPR to resist crushing relative to OP, data from in vitro and pharmacokinetic studies show that OPR's extended release features can be compromised, causing the product to '**dose dump**,' when subjected to other forms of manipulation such as cutting, grinding or chewing . . . In addition, certain data suggest that OPR **can more easily be prepared for injection** than OP."[57] [emphasis added].

In addition, in the FDA's Summary Review for Regulatory Action NDA 21-655 (January 7, 2011), the FDA determined that OPR would not be withdrawn from sale for safety reasons. The FDA determined that OPR is not sufficiently safer than OP.

> "While the new formulation has demonstrated a minimal improvement in resistance to tampering by crushing, thereby limiting the likelihood of abuse by crushing followed by ingestion, and by insufflation (snorting) to some degree, it can still be ...cut...rendering it readily abusable by ingestion and **intravenous injection**, and possibly still by insufflation; although whether...tablets can be snorted was not studied. Of more concern, when chewed...the new formulation **essentially dose dumps** like an immediate-release formulation."[58]

The FDA specifically recognized that OPR can be abused by small volume extraction. In a July 7, 2011 Summary Review by Dr. Bob Rappaport, it was reported that "Revopan [OPR] tablets can be cut [REDACTED] compromising the extended release properties of the product." It was also reported that "an *in vitro* study conducted by the Sponsor shows that **it might be easier** to prepare a solution for injection when using [REDACTED] that when using OPANA ER." [emphasis added]. "OPR can be readily prepared for injection, despite Endo's claim that OPR tablets have 'resistance to aqueous extraction (i.e., poor syringeability). In addition, certain data

[57] Docket FDA 2012-p.-0895, p. 5-6.
[58] FDA Reference ID: 2888730, p. 3.

202 Precision Road • Horsham, PA 19044 • Phone (267) 960-3300

suggest that OPR can more easily be prepared for injection than OP."[59] OPR formulations are easier to extract than OP formulations because OP formulations require an additional filtration step to remove non-water soluble tablet binders, such as microcrystalline cellulose, which are components of standard directly compressed tablets, whereas small volume extraction of OPR does not.

B. Objective Testing of the Breaking Strength of Reformulated OxyContin®'s Shows It to Be Lower Than Opana® for Which Abuse Deterrent Labeling Was Rejected

Purdue submitted evidence of breaking strength in support of abuse deterrence. Purdue's evidence is misleading because the breaking strength was determined using the incorrect test to determine formulation strength in relation to abuse deterrence. Purdue's "breaking strength" test is based on the EP method of testing "resistance to crushing of tablets" and a "breaking strength of at least 500 Newtons (N)." (See, e.g., U.S. Patent No. 8,114,383, listed in the Orange Book and having priority claim to 2003; and U.S. Patent No 8,309,060, listed in the Orange Book and priority claim to 2003).[60] The EP method uses two flat platens to crush the tablet. Using two flat platens is not meaningful in the context of abuse deterrence. A more appropriate test is one using at least one edged surface (e.g., blade and plate) to simulate chewing. Flattening the tablets using forces greater than 500 N (with traditional "tablet breaking force" definitions) does not address abuse deterrence potential in OCR.

The breaking force required to physically cut an OCR tablet was tested by PMRS. The OCR tablet was tested alongside an OPR formulation for comparison. The FDA denied abuse deterrent labeling to OPR, in part, because OPR dose dumps and is susceptible for intranasal abuse. The comparison also included each formulation's resistance to grinding.

Testing of the two formulations for breaking force (via blade and plate) resulted in the OCR dosage form having a breaking force of less than 100N. The OPR formulation had a breaking force of about 150N. Testing of the two formulations for grinding potential (via a commercial coffee grinder) resulted in the OCR dosage form yielding about 20% of particles smaller than 500 microns. The OPR dosage form yielded less than about 10% particles smaller than 500 micron. The OPR formulation was stronger and less susceptible to manipulation than OCR.

The reason the OPR formulation is stronger than the OCR formulation is because of the excipients and processing method. OPR contains PEO as the primary excipient. OPR is prepared by hot melt extrusion. Hot melt extrusion evenly heats the PEO to transform PEO into forming a strong matrix. OCR contains PEO as the primary excipient. OCR is prepared by a procedure including compressing the formulation together followed by heating the compressed formulation to cure the excipients, "compress and cure." Compress and cure only heats the outer portion of the compressed tablet forming a less strong matrix. As a result, the OPR formulation

[59] Docket FDA 2012-p.-0895, p.6.
[60] Purdue cites to and relies upon this inappropriate test to show generic tablets infringe the '383 patent. *See* In re: OxyContin® Antitrust Litigation, Purdue v. Teva, 994 F. Supp. 2d 367 (S. D. NY 2014).

202 Precision Road • Horsham, PA 19044 • Phone (267) 960-3300

is stronger, less susceptible to chewing and grinding than OCR, and thus less susceptible to oral or nasal abuse.

In the end, neither OCR or OPR prevent manipulation. The average biting force to orally chew a drug product is 300-500N. The breaking force of both OCR and OPR is much less, which makes both OCR and OPR susceptible to manipulation and dose dumping.

IV. THE "LIKING" STUDY RELIED UPON BY THE FDA IS SUBJECTIVE AND DOES NOT MEET THE REQUIRED CFR STANDARD OF ADEQUATE, WELL-CONTROLLED, ROBUST, RUGGED AND SCIENTIFICALLY RIGOROUS TESTING

As described above, OTR1018 tests the attractiveness of manipulated oxycodone formulations (OCR, OC) to known opioid abusers and assesses their *subjective* responses. FDA's Guidance recognizes that "liking" studies are subjective and lack rigor ("evaluating the subjective effects of drugs").[61]

"Liking" study OTR1018 cannot support a meaningful abuse deterrent effect because the "liking" study is subjective and lacks scientific foundation. The subjective responses of the study participants lack any correlation to measurable in vivo characteristics. Dr. Ed Sellers, the author of the "liking" study, describes the scientific foundation of "liking" studies at the September 11, 2015 Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM). Dr. Sellers is a clinical pharmacologist who has performed over 100 "liking" studies.

> "What are the data that informs the relationship of concentration and effect, both efficacy and safety. Now, . . . to Dr. Walsh's question on the Abuse Potential Study, if you take the concentrations at the time of Emax on the liking at the moment scale, it will probably come as no surprise to you that there actually is a **very, very poor correlation**, the correlation is 0.09." [emphasis added]
>
> "If you go to the therapeutic chronic dosing situation that we are looking at here, again you are **very hard pressed to find any data** that allows you to predict in a given patient what you are going to get." [emphasis added]
>
> "This isn't all that surprising because the sources of variation at the level of the brain and the receptor intercellular transduction membranes and so forth is really much, much larger than the variation you get with the kinetics."
>
> "That is because you have, of course, been chronic dosing situation, prior administration of opioids and of course you have a whole slew of genetic and epigenetic differences among individuals that basically take the population and make their sensitivity quite wide."

[61] Guidance, p. 12.

202 Precision Road • Horsham, PA 19044 • Phone (267) 960-3300

There is no statistical or meaningful difference between "liking" the "-finely crushed" OCR versus the "powdered" oxycodone HCl. The FDA concludes that the comparative difference is 80.4% vs. 89.3%, respectively.[62] The FDA provides no reasoning to justify the position that 80.4% vs. 89.3% represents a meaningful difference. In light of the overwhelming epidemiological evidence showing no meaningful abuse deterrent effect, no justification can exist.

Because the "liking" study relied upon by the FDA is subjective, biased and is not statistically meaningful, the "liking" study cannot be relied upon to support the position that Reformulated OxyContin® establish any meaningful reduction in abuse.

A. CDER Exclusivity Board Determined that OTR1018 Does Not Meet the FDA Standards of "Adequate and Well-Controlled" per 21 CFR 314 and Is Insufficient to Support OCR Abuse Deterrent Labeling.

Reformulated OxyContin® was approved for Abuse Deterrent Labeling by the FDA on April 16, 2013. Purdue petitioned the FDA for a grant of three (3) year exclusivity available to new formulations meeting certain requirements. On March 3, 2015, the Department of HHS, CDER Exclusivity Board granted Purdue 3-Year Exclusivity for OCR based solely on the "liking" study (OTR1018).

Per Section 505 of the FD&C Act, the standard for determining whether a supplement is eligible for 3-year exclusivity is that the approval of the supplement must be supported by a clinical investigation that is new, not a bioavailability study, "essential to approval" and conducted by the applicant.[63] The clinical investigation, however, does not need to meet the FDA standards of "adequate and well-controlled" per 21 CFR 314. "In the preamble to implement the exclusivity provisions of the Hatch-Waxman Act, 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."[64]

"The drug-liking study, OTR1018, qualifies as a 'clinical investigation' because it is . . . essential to the approval because there are no other data available to support approval of this supplement."[65] In a p. 5 footnote, the FDA noted that "S-14 supports the approval of labeling to specifically include data from Study OTR1018. **Moreover, according to the Division, no other data exists to support approval of this supplement.** [emphasis added].

The CDER Exclusivity Board finding did not indicate that OTR1018 was adequate, well-controlled or produced statistically significant results. The Board merely acknowledged that finely crushed OCR "was associated with a numerically lower mean and median drug liking score" than finely crushed OC.[66] The Board's finding, however, indicate that OTR1018 does not

[62] OxyContin® Package Insert 9.2, Table 2.
[63] FDA Reference ID: 3712567, p. 3.
[64] Id. p. 4.
[65] Id. p. 5.
[66] Id. p. 8.

202 Precision Road • Horsham, PA 19044 • Phone (267) 960-3300

meet the FDA standards of "adequate and well-controlled" per 21 CFR 314 and is insufficient to support OCR abuse deterrent labeling.

Because the "liking" study relied upon by the FDA is subjective and does not meet the required CFR standard of adequate, well-controlled, robust, rugged and scientifically rigorous testing, the "liking" study cannot be relied upon to support the position that Reformulated OxyContin® establish any meaningful reduction in abuse. As such, the "liking" study cannot support the three year grant of exclusivity to Purdue Pharma for Reformulated OxyContin®.

B. Post-Marketing Epidemiology Establishes Instead That Reformulated OxyContin® Has No Meaningful Abuse Deterrent Effects

FDA Guidance requires post-market studies "to determine whether the marketing of a product with abuse-deterrent properties result in meaningful reduction in abuse, misuse, and related adverse clinical outcomes, including addiction, overdose, and death in the post-approval setting."[67] Consistent with the FDA Guidance and as a condition for approval of NDA 022272, the FDA issued a post-marketing requirement to Purdue to conduct epidemiological studies to assess whether the changes made to the Reformulated OxyContin® formulation resulted in a decrease in misuse, abuse, addiction, overdose and death.

Purdue's epidemiology studies submitted to the FDA did not support an abuse-deterrent claim ("the findings were not mature enough to support an abuse-deterrent claim"[68]). As important, after 5 years post-approval, there exists a vast amount of data showing that OCR has no abuse deterrent effect.

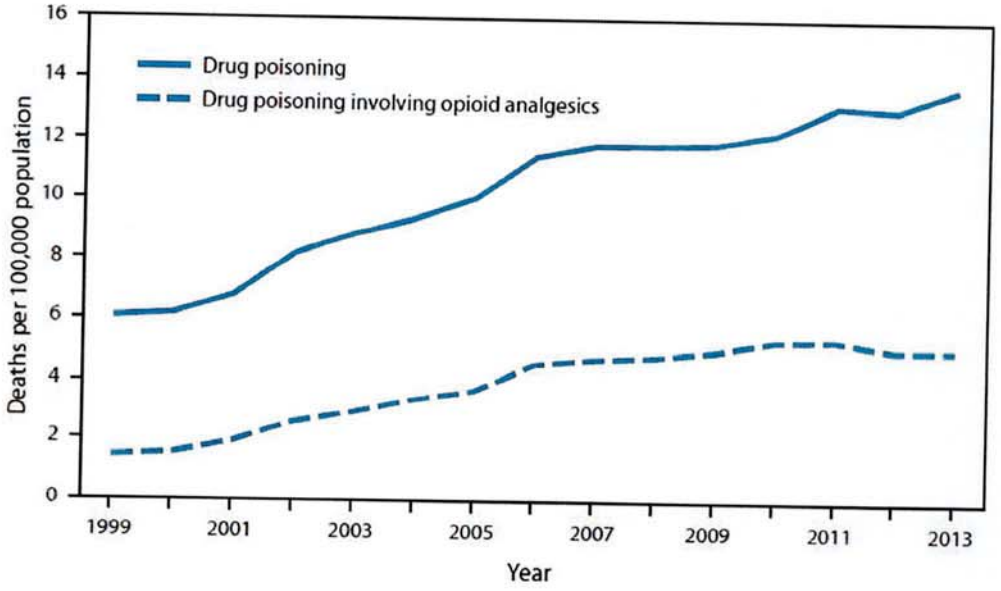
This fact is highlighted by Dr. Judy Staffa's (Director of Epidemiology at the FDA) statement at a recent drug advisory committee meeting (AADPAC on September 11, 2015). Judy Staffa, PhD, RPh Division Director, Division of Epidemiology II, Office of Pharmacovigilance and Epidemiology, OSE, CDER, FDA highlighted the lack of any meaningful reduction in abuse in response to a committee question during a discussion of abuse deterrent opioids at the September 11, 2015 Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM).

> "This is Judy Staffa, I guess I just wanted to make a cautionary comment that **we have not yet seen data that suggest that OxyContin® ADF has actually made a meaningful reduction in abuse.** With all due respect to the data that is out there, there is significant limitations. . . . The jury is still out as to how well abuse deterrent formulations have done in the real world, and it is not specific to OxyContin® it is all of them we just don't have the data we would like to see yet." [emphasis added]

[67] Guidance, p. 17.
[68] Id. p. 11.

202 Precision Road • Horsham, PA 19044 • Phone (267) 960-3300

Numerous third party reports show OCR and other similar abuse deterrent formulations have no meaningful abuse deterrence. For example, on January 16, 2015, the CDC published that in 2013 alone a total of 16,235 deaths involved opioid analgesics. From 1999 to 2013, the rate for drug poisoning deaths involving opioid analgesics nearly quadrupled from 1.4 to 5.1 per 100,000.



On November 18, 2015, an FDA News Release titled "FDA moves quickly to approve easy-to-use nasal spray to treat opioid overdose" stated that "drug overdose deaths, driven largely by prescription drug overdoses, are now the leading cause of injury death in the United States – surpassing motor vehicle crashes." "Combating the opioid abuse epidemic is a top priority for the FDA," said Stephen Ostroff, M.D., acting commissioner, Food and Drug Administration. "**We cannot stand by while Americans are dying.**" [emphasis added].

The FDA anticipates amending a drug product's abuse deterrent labeling based on the results of post-market studies if these post-market data fail to confirm that the abuse-deterrent properties result in a reduction in abuse. Here, the post-market data for Reformulated OxyContin® fails to establish any meaningful reduction in abuse. As such, the FDA should revoke the abuse deterrent labeling from Reformulated OxyContin® and restore NDA 020553 for original OxyContin®.

SUMMARY

The underlying principle supporting the FDA's actions to approve abuse deterrent labeling and, grant exclusivity for Reformulated OxyContin® and remove the NDA for original OxyContin® is the belief that Reformulated OxyContin® provides meaningful abuse deterrence and is safer than original OxyContin®. The analysis of the FDA ultimately hinged on a subjective "liking" study which was contrary to the FDA's own issued Guidance. Approval of potential abuse

202 Precision Road • Horsham, PA 19044 • Phone (267) 960-3300

deterrent formulations needs to be based on scientifically rigorous analysis of the opioid drug product with actual proof of abuse deterrence required through in-vitro chemical pre-market testing and by post-market epidemiological studies before an opioid drug product may be labeled abuse deterrent. The present system delays introduction of abuse deterrent formulations in that it imposes expensive and unnecessary "liking" studies that take years to complete and add no objective and scientifically rigorous analysis to the approval process.

As shown above, Reformulated OxyContin®, approved under the present standards, does not provide any meaningful abuse deterrence or improved safety because:

- the original data (in vitro testing and the "liking" study) does not support a meaningful abuse deterrent effect for Reformulated OxyContin®;
- oxycodone can be extracted from Reformulated OxyContin® by small volume extraction;
- Reformulated OxyContin® "dose dumps" when vigorously chewed;
- post-marketing epidemiology establishes that Reformulated OxyContin® has no abuse deterrent effect;[69] and
- in fact, it is easier to abuse Reformulated OxyContin® than it is to abuse original OxyContin®.

The effect of the FDA's decision to grant abuse deterrent labeling is to encourage the medical profession to prescribe it in the belief that it actually will have abuse deterrent protection.

> The number of annual opioid prescriptions written in the United States is now roughly equal to the number of adults in the population; given these numbers, simply reinforcing opioid-related activities that are within the FDA's traditional regulatory scope will not suffice to stem the tide.[70]

For the opioid epidemic to be brought under control, the FDA needs to require rigorous scientific proof of abuse deterrence in both small and large volume extraction and withhold abuse deterrent labeling until post-marketing studies in fact establish conclusively the ADF properties of a particular drug formulation. This will allow manufacturers to invest their resources in drug investigation and formulation rather than expensive and inconclusive pre-marketing "liking" studies and provide more flexibility rather than less to find formulations that are, as shown in the field, actually abuse deterrent. All of this will aid the rapid development of both branded and generic abuse deterrent formulations which as set forth in the above article is a stated goal of the FDA:

---

[69] OCR labeling encourages physicians to prescribe OCR to patients despite OCR being contraindicated because of drug abuse.

[70] *A Proactive Response to Prescription Opioid Abuse*, by Robert M. Califf, M.D., Janet Woodcock, M.D., and Stephen Ostroff, M.D, New England Journal of Medicine (2016), p. 1.

202 Precision Road • Horsham, PA 19044 • Phone (267) 960-3300

> The pharmaceutical industry has shown significant interest in developing abuse deterrent opioid formulations and the field is progressing rapidly. The availability of abuse deterrent formulations raises questions, including how to encourage their use in place of products without abuse-deterrent features and whether to modify criteria for the review and approval of oral opioid formulations that lack abuse-deterrent features or do not offer advantages in abuse deterrence relative to currently marketed products. We will continue to support abuse-deterrent formulations and encourage development of more effective abuse-deterrent features; we are also committed to convening advisory committees to consider new versions of non–abuse-deterrent opioids. In addition, draft FDA guidance on generic abuse-deterrent opioids will review many of the key issues; making this guidance available quickly is a high priority, since the availability of less costly generic products should accelerate prescribers' uptake of abuse-deterrent formulations.[71]

Interest of Pharmaceutical Manufacturing Research Services

PMRS submitted an Investigational New Drug Application (IND 124840) on July 17, 2015 under Section 505(i) of the FD&C Act for Oxycodone HCl ADF capsules. PMRS has received an NDA number for IND 124840. PMRS is the commercial manufacturer of Opana® (Oxymorphone HCl) tablets.

C. Environmental Impact

Petitioner claims a categorical exclusion from the requirements of an environmental assessment or environmental impact statement pursuant to 21 C.F.R. § 25.31.

D. Economic Impact

An economic impact statement will be submitted if requested by the Commissioner, pursuant to 21 C.F.R. § 10.30(b).

The remainder of this page was intentionally left blank

[71] Id. p. 4.

202 Precision Road • Horsham, PA 19044 • Phone (267) 960-3300

E. Certification

I certify that, to the best of my knowledge and belief, this petition includes all information and views upon which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Respectfully Submitted,

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