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October 21, 2013

Via Overnight Mail

Division of Dockets Management
Food and Drug Administration
Room 1061
5630 Fishers Lane
Rockville, MD 20852

CITIZEN PETITION

Dear Sir/Madam:

The undersigned, on behalf of Purdue Pharma L.P. ("Purdue"), submit this Citizen Petition pursuant to 21 C.F.R. §§ 10.30, 314.53, 314.94, 314.127, Part 320, and Section 505 of the Federal Food, Drug, and Cosmetic Act ("FDCA"), 21 U.S.C. § 355. As detailed below, Purdue is the holder of New Drug Application # 22-272 for OxyContin® (oxycodone hydrochloride extended-release) Tablets, a twice-a-day oral formulation of oxycodone formulated with physicochemical properties designed to deter misuse and abuse. Purdue was also the sponsor of New Drug Application # 20-553 for the original formulation of OxyContin, which was discontinued in 2010.[1]

Earlier this year, FDA determined that Purdue withdrew the original formulation of OxyContin from sale for reasons of safety, and stated that the Agency would not accept or approve abbreviated new drug applications that cite original OxyContin as the reference listed drug. FDA also approved new labeling for reformulated OxyContin that describes the results of Purdue's *in vitro* manipulation studies and drug-liking study. Finally, numerous FDA officials have stated that generic versions of reformulated OxyContin must also be abuse deterrent. Agency officials have not, however, described the data necessary to establish that proposed generic versions of OxyContin are sufficiently abuse deterrent to meet the standards for generic drug approval. Instead, the

[1] The drug product that is the subject of NDA # 20-553 will be referenced as "original" OxyContin for clarity. The current formulation approved in NDA # 22-272 will be referenced as "reformulated" OxyContin or simply OxyContin.

Agency has reportedly formed a working group to consider this issue and will be preparing a draft guidance document for comment by interested persons. This Petition is offered from the perspective of the developer of the abuse-deterrent formulation of OxyContin, and one of the independent expert consultants who assisted in the design and implementation of the successful testing program for that drug, consistent with the comments by FDA officials at the Abuse Deterrent Formulation Science Meeting, held on September 30 and October 1, 2013 in Rockville, Maryland (AD Science Meeting). Outlined below are the testing requirements Purdue believes are essential to assuring that any approved generic versions of OxyContin meet the standards set forth in the Federal Food, Drug and Cosmetic Act and preserve the public health benefits of the abuse-deterrent OxyContin formulation.

Proposed generic products that have not been shown, through the studies discussed in this Petition, to perform as well as reformulated OxyContin under conditions designed to simulate tampering, would not have the same risk-benefit profile as reformulated OxyContin, would not be as safe as reformulated OxyContin, and would not have the same performance characteristics as reformulated OxyContin. Such products cannot duplicate the "Abuse Deterrence Studies" section of OxyContin labeling, as required by the Hatch-Waxman Amendments and FDA's implementing regulations. Neither can those products be considered the "same dosage form" as OxyContin, "bioequivalent" to OxyContin, or to have inactive ingredients or formulations as safe as OxyContin. Simply put, such products cannot be considered "generic" versions of reformulated OxyContin.

This Petition is supported by the attached declaration of Dr. Edward J. Cone, a recognized expert in the evaluation of abuse-liability testing of abuse-deterrent drug product formulations. According to Dr. Cone, the abuse-deterrent attributes of reformulated OxyContin tablets cumulatively contribute to the deterrent effect of the product, in that each feature adds to the time and effort needed to prepare the tablets for abuse and reduces the reinforcing effects abusers seek.[2] For this reason, equivalent abuse deterrence can only be documented though comparative testing designed to evaluate equivalence on **each** critical feature of OxyContin. A less comprehensive testing strategy could lead to approval of a "generic" product which, even if formulated to have abuse deterrent features, is uniquely vulnerable to one or more particular manipulations – a fact that would quickly become widely known among the population of abusers and undermine the acknowledged benefits of OxyContin.[3] As a consequence, to protect the public health, it is important that any proposed generic copy of OxyContin be shown to have abuse-deterrent attributes at least as robust as those of OxyContin.

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2 Declaration of Edward J. Cone, Ph.D., at ¶ 13, attached hereto as Appendix A.

3 Appendix A, ¶ 14.

Therefore, Purdue requests that, prior to approval, all purported generic copies of reformulated OxyContin be subject to *in vitro* and *in vivo* tests sufficient to establish that the generic products have abuse-deterrent features which enable the generic product to perform as well as reformulated OxyContin when subjected to manipulations by individuals intent on abusing the product or by patients/caregivers inadvertently misusing the medication. Consistent with the testimony of CDER's Deputy Director Regulatory Programs, Dr. Douglas Throckmorton, during a June 2013 Congressional hearing, and echoed by Dr. Andre Raw of the Office of Generic Drugs at the AD Science Meeting, this Petition advocates an approach that turns on the demonstrated functional performance of proposed generic products, rather than equivalency of technology or similarity of ingredients. Approval of a generic version of OxyContin that has not been shown, through the tests specified herein, to have equivalent abuse deterrent attributes, would not only compromise the public health but would also be impermissible under Section 505(j) of the Act and the Administrative Procedure Act.[4]

The undersigned previously submitted a Citizen Petition dated July 13, 2012, Docket No. FDA-2012-P-0760, refiled with non-substantive changes on August 28, 2012, Docket No. FDA-2012-P-0939. Those petitions addressed similar issues and requested similar actions as the present petition, and are expressly incorporated herein by reference. The July 13, 2012 petition has not been granted or denied. The August 28, 2012 petition was the subject of a non-substantive "denial" on January 23, 2013, because no generic applications were otherwise ready for approval at that time. On February 22, 2013, the undersigned filed a Petition for Reconsideration of the January 23, 2013 action, pointing out the continuing and compelling need for the FDA to address and substantively rule on the issues raised in these petitions, despite the current status of pending generic applications. There has been no response to the February 22, 2013 Petition for Reconsideration. Therefore, the July 13, 2012 and August 28, 2012 Petitions, and the February 22, 2013 Petition for Reconsideration remain pending before the Agency.[5]

The current Petition updates the factual record with (1) the latest epidemiologic data and other relevant information published since July 2012; (2) critically relevant Agency actions and findings since January 2013; (3) an updated Declaration from Dr. Edward J. Cone; and (4) updated recommendations regarding the tests that must be conducted to demonstrate equivalence to reformulated OxyContin. For the reasons stated in our Petition for Reconsideration, we believe that an expedited announcement of proper standards for evaluating the equivalence of proposed generic versions of abuse-deterrent drug products is warranted, and submit this Petition to assist in that regard.

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[4] 5 U.S.C. § 706(2)(A).

[5] The undersigned have not, either explicitly or implicitly (*e.g.*, by filing the current Petition), withdrawn the above-referenced July 2012, August 2012 or February 2013 Petitions.

Action Requested

Purdue requests that the Food and Drug Administration take the following actions with respect to abbreviated new drug applications citing OxyContin (NDA # 22-272) as the Reference Listed Drug:

(1) Adopt and announce a guidance detailing *in vitro* and *in vivo* tests sufficient to establish that proposed generic products have equivalent abuse-deterrent properties and can be expected to perform as well as reformulated OxyContin when subjected to manipulations by individuals intent on abusing the product or by patients/caregivers inadvertently misusing the medication, including at least the following:[6]

(a) Tablet manipulation studies to determine the resistance of the proposed generic formulation to methods of reducing tablets to particles using a variety of commonly available tools, and to establish the time and effort required to reduce the proposed generic tablets to fine particles;

(b) *In vitro* small and large volume extraction and dissolution studies on intact tablets and on standardized particle sizes of manipulated tablets, using an appropriate range of solvents, conditions, and pretreatments;

(c) *In vitro* studies measuring the syringability and injectability of tablet contents, extracted by standardized procedures;

(d) *In vitro* studies measuring the ability to create and extract free oxycodone base from the tablets;

(e) *In vitro* smoking simulation studies measuring the ability to vaporize oxycodone from fine particles prepared from the tablets;

(f) An *in vivo* bioequivalence/non-inferiority study with clinical endpoints evaluating the abuse potential of orally ingested manipulated tablets (ingested after chewing, or after reducing the tablets to fine or coarse particles), providing measures of T_{max}, C_{max}, and AUC, and liking; and

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[6] Since the time Purdue first began discussing a reformulated version of OxyContin with FDA, the Agency has indicated that publicly available information about the testing of the formulation should not include specific details that might be used by abusers to intentionally extract oxycodone from the product. Purdue shares this concern and therefore urges that the guidance not be so detailed as to provide a "roadmap" to would-be abusers. To the extent that more detailed information concerning recommended test methodology is required, the Agency may reasonably conclude that such additional detail should be provided only in confidential communications with potential NDA and ANDA applicants.

(g) An *in vivo* bioequivalence/non-inferiority study with clinical endpoints evaluating the abuse potential of insufflated fine particles, providing measures of (PK measures of T_{max}, C_{max}, and AUC, and liking; and

(h) Additional *in vitro* and/or *in vivo* tests necessary to evaluate any potential formulation-specific vulnerabilities associated with physical and chemical features of the generic product, using reformulated OxyContin as a control.

All of these tests should be comparative, using the reference listed drug OxyContin and powdered oxycodone API, as controls. The guidance should require, with respect to each *in vitro* and *in vivo* test, that generic products pass statistical analyses which demonstrate that they exhibit no greater rate or extent of oxycodone release or relative abuse potential than OxyContin.

(2) Refuse to approve any ANDA citing OxyContin (NDA # 22-272) as the Reference Listed Drug that (a) does not include data from the *in vitro* and *in vivo* tests requested in (1) above, or (b) includes data from such tests which fail to meet the acceptance criteria requested in (1) above.

(3) Modify the draft bioequivalence guidance on oxycodone extended release tablets[7] to reflect those test requirements.

Statement of Grounds

I. Factual and Procedural Background

A. Development and *In Vitro* Testing of Reformulated OxyContin

As reports of abuse of the original formulation of OxyContin abuse became prevalent, Purdue took a number of steps to address abuse and diversion, as well as inadvertent misuse by patients or their caregivers, including development work on a new formulation of OxyContin.[8] NDA # 22-272 for reformulated OxyContin was submitted in November 2007. The NDA included data showing that the new formulation is

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[7] *See* Office of Generic Drugs, *Draft Guidance on Oxycodone Hydrochloride, Extended Release Tablets*, (July 2010), available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM220198.pdf.

[8] The new formulation is covered by U.S. patents and patent applications, including patents listed in the Orange Book by Purdue for OxyContin. Purdue reserves all rights in its patents and patent applications.

bioequivalent to the original formulation of OxyContin as well as *in vitro* data characterizing the physicochemical properties of the tablets.

At a joint meeting in May 2008, the Anesthetic and Life Support Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee reviewed the *in vitro* data submitted with the NDA and concluded the available data were not adequate to evaluate whether reformulated OxyContin is likely to reduce abuse, misuse, or diversion.[9]

Subsequently, FDA issued a Complete Response Letter ("CRL") requesting additional studies to characterize the physicochemical properties of reformulated OxyContin. In the CRL, the Agency directed that those studies incorporate several elements including (a) blinded testing, preferably by an independent third party; (b) new, validated, reproducible test methods developed with the input of experts on the methods used by abusers to extract oxycodone from OxyContin; (c) assessment of protocols and study data by experts in extraction techniques; (d) a study evaluating release of oxycodone when the tablet is chewed; (e) studies evaluating oxycodone release from all strengths of crushed tablets; and (f) studies on all tablet strengths assessing particle size distribution resulting from various grinding techniques; and (g) assessment of suitability of ground tablets for insufflation. Purdue was required to design and conduct these additional studies before reformulated OxyContin would be approved.[10]

As directed by FDA, Purdue consulted independent experts in drug abuse, tablet tampering, and analytical pharmaceutics to guide and supervise the design, execution, analysis, and interpretation of a rigorous *in vitro* test program intended to satisfy FDA requirements. With respect to experimental design, experts provided input on the elements to include in each protocol to yield reliable scientific data. Experts also identified those real world tamper techniques that should be simulated through the *in vitro* test program. One of the primary advisors to Purdue in this regard was Dr. Edward J. Cone, whose Declaration is attached hereto as Exhibit 1.[11]

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[9] Summary Minutes of the Joint Meeting of the Anesthetic and Life Support Drugs and Drug Safety and Risk Management Advisory Committee of May 5, 2008, available at: http://www.fda.gov/ohrms/dockets/ac/08/minutes/2008-4356m1-final.pdf.

[10] *See* Division Director Summary Review for Regulatory Action, NDA # 22-272, Bob A. Rappaport, M.D., pp. 3-4 (Dec. 30, 2009), available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022272s000MedR.pdf.

[11] Also enclosed is Dr. Cone's Declaration of July 11, 2012, originally provided in support of the Petitions docketed as FDA-2012-P-0760 and FDA-2012-P-0939, and his March 2009 Report prepared in connection with his initial consultation on the appropriate means of evaluating the abuse-deterrent properties of reformulated OxyContin. *See* Exhibit A-2.

Based on input from these independent experts, and in accordance with the requirements of the CRL, Purdue conducted an additional extensive battery of *in vitro* experiments to characterize the physicochemical properties of reformulated OxyContin. A detailed description of Purdue's development of a model for the *in vitro* laboratory assessment of reformulated OxyContin has been published in a peer-reviewed journal.[12] The *in vitro* test battery reflects a systematic approach to evaluate a range of potential tampering methods that might be attempted by drug abusers. The overall goal of this approach was to define the strengths and failure limits of reformulated OxyContin after physical and chemical manipulations. The resulting data provided a systematic basis for assessing the overall abuse deterrent properties of the formulation relative to the properties of original OxyContin.

The *in vitro* protocols which resulted from applying this carefully designed, iterative approach encompassed multiple types of studies.[13] These studies collectively tested a wide range of physical and chemical methods to manipulate tablets – methods known or anticipated to be used inadvertently by patients/caregivers or intentionally in the setting of purposeful misuse or abuse. Original OxyContin was included in each experiment for comparison.

The *in vitro* data from these studies indicated that reformulated OxyContin is less susceptible to manipulation than the original formulation under many test conditions, and not more susceptible to tablet manipulation than the original formulation under any test condition.[14]

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[12] Cone, E.J., *et al., An iterative model for in vitro laboratory assessment of tamper deterrent formulations,* Drug and Alcohol Dependence, 131 (2013), 100-105, published online Jan. 17, 2013, available at: http://www.sciencedirect.com/science/article/pii/S0376871612004826 and attached hereto as Exhibit A-4.

[13] In particular, these groups of studies are: fractionalization of tablets; extraction; dissolution in ethanol; extraction in advanced solvents; syringeability and injectability; extraction after vaporization; complex extraction of oxycodone using advanced techniques; and complex extraction with advanced solvents using liquid phase extraction. Additional detail about these groups of studies is available on FDA's website. *See* Purdue Pharma L.P., FDA Advisory Committee Briefing Document on NDA 22-272 (reformulated OxyContin® tablets) (Sept. 24, 2009) at 20-24, 4, 9, available at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndLifeSupportDrugsAdvisoryCommittee/UCM183205.pdf. Passages have been redacted by FDA in the posted version of this document, so as to avoid providing would-be abusers with information that could facilitate abuse of reformulated OxyContin.

[14] Purdue Pharma L.P., FDA Advisory Committee Briefing Document on NDA 22-272 (reformulated OxyContin® tablets) (Sept. 24, 2009) at 20-24, 4, 9, available at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndLifeSupportDrugsAdvisoryCommittee/UCM183205.pdf.

Purdue also initiated *in vivo* pharmacokinetic and abuse potential studies of reformulated OxyContin. Data from these four clinical studies, the results of which were originally submitted to FDA in the fall of 2010, have been made available publicly in abstracts, posters, and journal articles. These four studies included one pharmacokinetic study that determined the bioavailability of the tablets administered intact orally and, after manipulation, orally and intranasally, and three abuse potential studies examining the drug's pharmacokinetic profile, alongside various subjective measures, with and without manipulation. Each study is described in Appendix B and in the attached abstracts, posters, and articles.

FDA convened a second joint Advisory Committee meeting on September 24, 2009, to review the new *in vitro* data characterizing the physicochemical properties of the new formulation. The Committee determined that the data demonstrated an incremental increase in tamper-resistance, although the product could still be abused or misused by taking intact tablets.[15]

The NDA for reformulated OxyContin was approved on April 5, 2010.[16]

B. Launch and Post-Marketing Study of Reformulated OxyContin

Following approval, Purdue ceased shipment of the original formulation and, in August 2010, began shipment of reformulated OxyContin. By December 24, 2010, 92.3% of total OxyContin prescriptions dispensed were filled with the new formulation, increasing to over 99% by October 2011.

Purdue designed an epidemiologic study program with the assistance of external experts, which is intended to generate a comprehensive picture of the effects of the reformulation. In particular, the objective of the epidemiologic study program is to assess the effects on four outcomes in the real world setting: abuse and its consequences of addiction, overdose and death; diversion; medical errors among patients; and adverse effects from unintentional, inadvertent exposures. The program consists of eleven epidemiologic studies. The studies use different databases and examine different

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[15] A memorandum authored by the Director, Division of Anesthesia, Analgesia and Rheumatology Products describes the conclusions of the Committee. Summary Review for Regulatory Action, NDA # 22-272, R. Rappaport, M.D. (Dec. 30, 2009) at 6, available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022272s000MedR.pdf.

[16] A press release and Patient Safety News Video describe FDA's initial conclusions concerning the potential advantages of reformulated OxyContin. *FDA Approves New Formulation for OxyContin* (April 5, 2010), available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm207480.htm; FDA Patient Safety News, *New Formulation for OxyContin*, Show # 99, June 2010, links and transcription available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/psn/transcript.cfm?show=99.

populations for a comprehensive assessment of effects on the four outcomes of interest. The design of most of these studies is to assess changes from before to after introduction of reformulated OxyContin and compare changes observed for OxyContin to changes for comparator prescription opioids across these same time periods.[17]

Data from several epidemiologic studies have been made available publicly in abstracts, posters, and presentations submitted to professional associations, and in published articles. Information on these studies, as well as other publicly available data addressing the effects of the reformulation, is provided in Appendix C.

Collectively, available data demonstrate that reformulated OxyContin is having the effect Purdue intended when it undertook development work on the new formulation. These data show that the introduction of reformulated OxyContin has resulted in a decrease in misuse and abuse of OxyContin, and their consequences. Specifically, the epidemiologic study data show:

- Reductions in rates and frequency of OxyContin abuse
- Reductions in abuse through non-oral routes (*i.e.* injecting, snorting, and smoking)
- Reductions in drug diversion activity involving OxyContin
- Reduction in intentional poisonings and calls to poison centers reporting abuse involving OxyContin
- Reduction in unintentional poisonings involving OxyContin, , particularly therapeutic errors affecting patients and accidental exposures affecting toddlers
- Reduction in adverse events and medication errors associated with tablet manipulation.

The epidemiologic studies show significant reductions in exactly those types of abuse and misuse that reformulated OxyContin was anticipated to affect based on the results of the comprehensive battery of *in vitro* studies conducted prior to approval of NDA # 22-272, indicating Purdue's *in vitro* experiments have predictive value.

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[17] A poster and abstract describing the rationale for the design of the Purdue epidemiologic study program were presented at the International Conference on Pharmacoepidemiology & Therapeutic Risk Management. *See* Coplan, P.M., *Design of a Post-Marketing Study Program to Assess the Effects of a Reformulated Extended-Release Oxycodone Tablet on its Abuse,* presented at 28th International Conference on Pharmacoepidemiology & Therapeutic Risk Management, August 23-26, 2012, Pharmacoepidemiology and Drug Safety 2012; Vol. 21 (Supp. 3), p. 446, Abstract # 963 and Poster, abstract available at http://onlinelibrary.wiley.com/doi/10.1002/pds.3324/pdf, at p. 446, attached hereto as Exhibit 1. *See also* Purdue Pharma L.P., Advisory Committee Briefing Materials for Joint Meeting of the ALSDAC and SDaRM on October 21 and 22, 2010, NDA 22272 OxyContin® (oxycodone hydrochloride) Controlled-Release Tablets at 2-3, available at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndLifeSupportDrugsAdvisoryCommittee/UCM230110.pdf.

C. FDA Guidance Addressing Abuse-Deterrent Opioids

In January 2013, FDA issued a draft guidance intended to assist industry in developing new formulations of opioid drugs with abuse-deterrent properties. The Agency acknowledged, in announcing the draft guidance, that development of opioids formulated to deter abuse is "a high public health priority."[18]

The guidance categorizes abuse-deterrent formulations into six potential types. Reformulated OxyContin falls within the "Physical/Chemical barriers" category, described as: "Physical barriers can prevent chewing, crushing, cutting, grating, or grinding. Chemical barriers can resist extraction of the opioid using common solvents like water, alcohol, or other organic solvents. Physical and chemical barriers can change the physical form of an oral drug rendering it less amenable to abuse." Other categories of abuse-deterrent formulations recognized in the guidance are "Agonist/Antagonist combinations," "Aversion," "Delivery System," "Prodrug," and "Combination" incorporating two or more of the other methods.[19]

Three categories of premarketing studies are discussed in the guidance: laboratory-based *in vitro* manipulation and extraction studies (Category 1); pharmacokinetic studies (Category 2), and clinical abuse potential studies (Category 3). The guidance provides that, in most cases, data from each of the three categories are necessary for a full and scientifically rigorous understanding of the impact of abuse-deterrent technologies on a product's abuse potential. Describing the interrelationship between the three categories of studies, the guidance explains that "[t]he results of Category 1 studies influence the design of Category 2 pharmacokinetic studies, and the results of Category 2 studies influence the need for Category 3 studies of human abuse potential and the designs and goals of these studies."[20]

The guidance provides that premarket evaluation of the abuse-deterrent attributes of an opioid formulation must be scientifically rigorous. Basic design requirements include use of appropriate positive controls and comparator drugs, appropriate outcome measures, meaningful statistical analyses of the data, and enrollment of appropriate study subjects. Premarketing studies should also "take into consideration the most common

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18 *Guidance for Industry: Abuse-Deterrent Opioids – Evaluation and Labeling,* Draft Guidance (Jan. 2013), available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM334743.pdf ("*AD Guidance*").

19 *AD Guidance* at 2-3.

20 *AD Guidance* at 3.

routes of abuse for the opioid." The guidance includes detailed discussions of each of the three categories of studies.

The guidance also discusses a fourth category of studies: postmarketing epidemiologic studies designed to assess the impact of the formulation on abuse and abuse-related clinical outcomes (addiction, overdoses, poisonings, and death).

The final section of the guidance discusses potential labeling describing the results of Category 1 – 4 studies. The guidance acknowledges the importance of labeling describing demonstrated abuse-deterrent properties and encourages sponsors to seek approval of labeling providing the results of pre- and postmarketing studies designed to evaluate abuse deterrence. Label claims will be permitted based only on "robust, compelling, and accurate data and analysis" when the "data predict or show that a product's potentially abuse-deterrent properties can be expected to, or actually do, result in a significant reduction in that product's abuse potential."[21]

The guidance describes four tiers of claims that may be used to describe the abuse-deterrent attributes of a product:

Tier 1: The Product is Formulated with Physicochemical Barriers to Abuse
Tier 2: The Product is Expected to Reduce or Block Effect of the Opioid When the Product is Manipulated
Tier 3: The Product is Expected to Result in a Meaningful Reduction in Abuse
Tier 4: The Product has Demonstrated Reduced Abuse in the Community.[22]

In order to include Tier 1, 2, or 3 claims in product labeling, a sponsor generally must provide data from Categories 1, 2, and 3 studies, *i.e., in vitro,* pharmacokinetic, and abuse potential studies. The guidance indicates FDA is not able to specify the magnitude of effect that is necessary to support each type of claim; accordingly, proposed claims will be evaluated on a case-by-case basis in light of the data presented.

D. FDA Assessment of Data Evaluating The Abuse-Deterrent Properties of Reformulated OxyContin

In response to a number of Citizen Petitions filed on behalf of generic manufacturers and an NDA supplement filed by Purdue, FDA conducted a multidisciplinary review of the scientific data characterizing the abuse-deterrent properties of reformulated OxyContin. In an April 2013 memorandum summarizing the

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21 *AD Guidance* at 17.

22 *AD Guidance* at 18.

conclusions of this extensive review, Dr. Throckmorton described Purdue's *in vitro* test methodology as follows:

> The in vitro testing of the physical properties of [reformulated OxyContin] was extensive and rigorously conducted, and the effects shown provide a strong basis for predicting an effect of [reformulated OxyContin] on route-specific abuse. The studies were appropriate for a formulation that is focused on physical changes to deter abuse and misuse. The testing of the physical properties was robust in that it was also sufficient to reveal how the current formulation could be defeated (e.g., vigorous chewing or robust mechanical grinding).

Dr. Throckmorton described the conclusions from the *in vitro* data as follows:

> Overall, the in vitro studies demonstrate that manipulation of [reformulated OxyContin] tablets is more difficult compared with the manipulation of [original OxyContin] tablets. Compared with the [original] formulation, the extended-release mechanism of [reformulated OxyContin] tablets requires a higher amount of effort, time, experience and tools to defeat making it more difficult to create a fine powder for insufflations. This is important because particle size may influence the rate of opioid release from the manipulated product. For extraction for intravenous abuse, [reformulated OxyContin] is particularly challenging as it turns into a viscous gel that is resistant to injection. This feature may make abuse via insufflation more difficult also, but whether this is so cannot be measured using mechanical testing methods only and should be considered in the context of the other categories of testing below. Oxycodone in both the [original] and [reformulated] formulations is not appropriate for vaporization (e.g., smoking) as the oxycodone degrades at temperatures close to where vaporization occurs. To summarize the results, the in vitro data suggest that [reformulated OxyContin] represents an improvement over [original OxyContin] in that it increases the ability of [reformulated OxyContin] to resist crushing, breaking, and dissolution. The in vitro data also demonstrate that [reformulated OxyContin] has physicochemical properties expected to make abuse by injection difficult. The in vitro data provide support, together with other categories of data below, that [reformulated OxyContin] has physicochemical properties that are expected to reduce abuse via the intranasal route.

With respect to the clinical abuse-potential study evaluating insufflation of manipulated tablets, Dr. Throckmorton concluded as follows:

> The data from the clinical studies, along with support from the in vitro and other data, indicate that [reformulated OxyContin] has physicochemical

properties that are expected to reduce abuse via insufflation. That is, the reformulation resulted in reduced attractiveness for insufflation of the manipulated [reformulated OxyContin] to individuals experienced in the abuse of opioids when compared with manipulated [original OxyContin.][23]

E. FDA Approval of New Labeling Providing Information on the Abuse-Deterrent Properties of Reformulated OxyContin

On April 16, 2013, FDA approved new OxyContin labeling that describes the results of Purdue's *in vitro* manipulation and extraction studies and clinical abuse potential study based upon the multidisciplinary review summarized in Dr. Throckmorton's memorandum.[24] This approval applied the principles set out in the January 2013 draft guidance, and allowed statements describing reduced abuse liability for OxyContin. The new section of the label, entitled "Abuse Deterrence Studies," first describes the *in vitro* studies conducted as follows:

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

The new label text also includes a detailed description of Purdue's *in vivo* insufflation abuse-potential study.[25] Results are provided in a table, and described as follows:

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

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[23] Memorandum to J. Woodcock, MD, Director, CDER from D. Throckmorton, MD, Deputy Director for Regulatory Programs, CDER (April 16, 2013) at pp. 9, 4, 5-6, available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/022272Orig1s014_ODMemo.pdf.

[24] *See* OxyContin Package Insert (April 2013), Section 9.2, available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022272Orig1s014lbl.pdf.

[25] This study is described in Section I of Appendix B, and in Exhibit B-1.

The newly approved labeling also includes the following summary statement:

> The *in vitro* data demonstrate that OxyContin has physicochemical properties expected to make abuse via injection difficult. The data from the clinical study, along with support from the in vitro data, also indicate that OxyContin has physicochemical properties that are expected to reduce abuse via the intranasal route. However, abuse of OxyContin by these routes, as well as by the oral route is still possible.
>
> Additional data, including epidemiological data, when available, may provide further information on the impact of the current formulation of OxyContin on the abuse liability of the drug. Accordingly, this section may be updated in the future as appropriate.
>
> OxyContin contains oxycodone, an opioid agonist and Schedule II controlled substance with an abuse liability similar to other opioid agonists, legal and illicit, including fentanyl, hydromorphone, methadone, morphine, and oxymorphone. OxyContin can be abused and is subject to misuse, addiction, and criminal diversion *[See Warnings and Precautions (5.1) and Drug Abuse and Dependence (9.1)]*.

In the framework of the January 2013 draft guidance, the newly approved labeling statements are Tier 1 and Tier 3 claims. FDA consideration of the labeling included evaluation of data from Category 1, 2, 3, and 4 studies.[26]

> FDA described its action on the new label as follows:
>
> The FDA has determined that the reformulated product has abuse-deterrent properties. The tablet is more difficult to crush, break, or dissolve. It also forms a viscous hydrogel and cannot be easily prepared for injection. The agency has determined that the physical and chemical properties of the reformulated product are expected to make the product difficult to inject and to reduce abuse via snorting. However, abuse of OxyContin by these routes, as well as the oral route, is still possible. The reformulated product also may reduce incidents of therapeutic misuse, such as crushing the product to sprinkle it onto food or to administer it through a gastric tube. When FDA finds that a new formulation has abuse deterrent properties, the

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[26] *See generally,* FDA Review, NDA 22-272, Supplement 14, available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/022272Orig1s014TOC.cfm.

agency has the authority to require generics to have abuse-deterrent properties also.[27]

The Agency's blog provided similar information:

> [W]e approved updated labeling for Purdue Pharma's reformulated version of OxyContin extended-release (ER) tablets. The new labeling describes the product's abuse-deterrent properties. These physical and chemical properties make it more difficult to crush, break, or dissolve the tablets. These properties are expected to make abuse by injection difficult and to reduce abuse by snorting. This is the first time we have approved such language in opioid drug labeling, and we made this determination after carefully reviewing the available science.[28]

F. FDA Determination that Original OxyContin Was Withdrawn from Sale For Reasons Of Safety

At the same time as FDA approved revised labeling for reformulated OxyContin concerning its abuse-deterrent properties, the Agency also announced its conclusion that Purdue had withdrawn the original formulation of OxyContin from sale for reasons of safety. This determination was also based upon the multidisciplinary review summarized in Dr. Throckmorton's memorandum, and was made in response to several Citizen Petitions submitted on behalf of companies seeking to market generic versions of original OxyContin.[29]

Following an "extensive review" of the Category 1, 2, 3, and 4 data concerning reformulated OxyContin, FDA concluded that the new formulation has safety advantages over original OxyContin, specifically:

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[27] FDA approves abuse-deterrent labeling for reformulated OxyContin, *Agency will not approve generics to original OxyContin* (April 16, 2013), available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm348252.htm.

[28] *The Science of Abuse-Deterrence – Progress Toward Creating Safer Opioids*, Douglas C. Throckmorton, M.D., Deputy Director for Regulatory Programs, CDER (April 16, 2013), available at: http://blogs.fda.gov/fdavoice/index.php/2013/04/the-science-of-abuse-deterrence-progress-toward-creating-safer-opioids/.

[29] *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 Fed. Reg. 23273 (April 18, 2013). *See* Docket Nos. FDA-2011-P-0473, FDA-2010-P-0540, FDA-2010-P-0526, and FDA-2001-P-0473.

- Increased ability to resist crushing, breaking, and dissolution using a variety of tools and solvents,
- Formation of a viscous hydrogel when subjected to an aqueous environment, and
- Lower drug liking of insufflated finely crushed reformulated OxyContin compared to finely crushed original OxyContin.[30]

The Agency further determined that the physicochemical properties of reformulated OxyContin are expected to "make abuse via injection difficult . . . [and] reduce abuse via the intranasal route," and "may deter certain types of misuse in therapeutic contexts." Correspondingly, FDA concluded that the original formulation of OxyContin poses an increased potential for abuse by certain routes of administration, compared to reformulated OxyContin, and thus "the benefits of original OxyContin no longer outweigh its risks."[31]

FDA determined that Purdue withdrew the original formulation from sale for reasons of safety. As a result, the Agency announced that it would not accept or approve ANDAs that cite original OxyContin as the reference listed drug.[32]

G. FDA Determination that Original Opana ER Was Not Withdrawn from Sale for Reasons of Safety Or Effectiveness

Shortly after FDA concluded that original OxyContin was withdrawn from sale for reasons of safety, the Agency responded to a Citizen Petition seeking a similar determination for the original formulation of another opioid that had been reformulated for purposes of making abuse and misuse more difficult. In that situation, the Agency concluded that the original formulation of Opana® ER (oxymorphone HCl) Extended-Release Tablets was not withdrawn from the market for reasons of safety or effectiveness. Accordingly, the Agency announced that generic products citing the original formulation of Opana ER may remain on the market, and new generic copies of that original formulation may be approved.[33]

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30 78 Fed. Reg. at 23274.

31 *Id.*

32 78 Fed. Reg. at 23275.

33 FDA Response to Citizen Petition, Docket No. FDA-2012-P-0895 (May 10, 2013), available at: http://www.regulations.gov/#!documentDetail;D=FDA-2012-P-0895-0014 ("Opana Citizen Petition Response"); *see also 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 Efficacy,* 78 Fed. Reg. 38053 (June 25, 2013).

Opana ER uses the same polymer for its sustained-release matrix as OxyContin, polyethylene oxide. And, similar to OxyContin, the polyethylene oxide in Opana ER is heated to provide its hardness. Nonetheless, after an "extensive, science-based review,"[34] FDA determined that available data do not show that original Opana ER has a greater potential for abuse compared to reformulated Opana ER. In particular, FDA reached the following conclusions based on the data:

- Reformulated Opana ER is more resistant to crushing than original Opana ER, but *in vitro* and pharmacokinetic data show that the reformulated version'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, followed by swallowing.
- Reformulated Opana ER can be readily prepared for injection, and certain data suggest that reformulated Opana ER may be more easily prepared for injection than original Opana ER.
- It appears that reformulated Opana ER can be prepared for insufflation using commonly available tools and methods.
- It is not possible to draw meaningful conclusions from the postmarketing investigations because they are inconclusive, preliminary, and deficient in other respects.[35]

The Agency rejected the sponsor's argument that the abuse-deterrent properties of reformulated Opana ER and reformulated OxyContin are virtually identical, and therefore warranted the same regulatory determinations. FDA explained that such decisions would be made on a case-by-case basis based on the totality of evidence for the particular drug at issue. The Agency also noted that there were differences between reformulated Opana ER and reformulated OxyContin and the data available for each product, and that these differences justified different conclusions on the withdrawal-for-safety question.[36]

In June 14, 2013 Congressional testimony, Dr. Throckmorton explained the basis for FDA's different conclusions with respect to OxyContin and Opana ER as follows:

> In both cases we looked at the available data on that product and specific [sic] the new formulation and then looked at it in comparison with the earlier formulation, the formulation that had been originally developed and asked questions about whether or not the new technology promised to reduce abuse. We think it is terribly important that this bar, this bar of

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[34] FDA Statement: Original Opana Relisting Determination (May 10, 2013), available at: http://www.fda.gov/Drugs/DrugSafety/ucm351357.htm ("Opana Statement").

[35] Opana Citizen Petition Response at pp. 5-8.

[36] Opana Citizen Petition Response at pp. 7-8.

concluding something is abuse-deterrent be high enough to be worth developing, make it an incentive, make it something that we can reward in labeling terms to make those products attractive for manufacturers to take the time and money to develop.

In the case of OxyContin when we looked at the data, there were important aspects of the new formulation that really did predict it was going to be harder to abuse. One particular one is when people tried to make it ready to inject, it turns into a gel that is just physically impossible to inject into someone's arm. You know, some of that testing involved using people who are addicts trying to, you know, do things that, you know, that would allow this to be used and they were unable to do it.

Now, so those sorts of evidence strongly suggest that a product with those formulation characteristics is going to have reduced attractiveness to abusers in the real world. We are tracking that real-world experience now going forward. On the other hand, when we looked at the totality of the data around the Opana ER product, we didn't see data of that same kind, data that suggested that that product was really going to be meaningfully harder to abuse, meaningfully meaning we would see less abuse. . . .[37]

H. FDA Statements on Requirements for Generic Versions of Abuse-Deterrent Formulations

In the same June 2013 Congressional testimony, Dr. Throckmorton provided the following answer to a question from Congressman Schakowsky about the impact of abuse-deterrent product development on the availability of generic drug products:

And this is back to the discussion of the balances, you know, that need to be kept in mind as we think about addressing this abuse crisis. So in this case we have the necessary balance between incentivizing the development of abuse-deterrent formulations that work. We want to have opioids in formulations that deter abuse. I believe that is in everyone's best interest to find a way to incentivize that while at the same time recognizing the impact and importance of the generics in the U.S. market, currently well more than 75 percent of the total prescriptions, et cetera.

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[37] Preliminary Transcript of Hearing, "Examining the Federal Government's Response to the Prescription Drug Abuse Crisis"; June 14, 2013, House of Representatives, Subcommittee on Health, Committee on Energy and Commerce, Washington, DC, pages 80-82, available at http://democrats.energycommerce.house.gov/sites/default/files/documents/Transcript-Health-Rx-Drug-Abuse-2013-6-14.pdf.

Accomplishing that balance is something that the FDA is thinking and working very hard on. Our first action was earlier in the year when we put out the guidance laying out how we would try to incentivize the development of new formulations. Following up on that, we are now thinking about ways to develop guidance on abuse deterrent formulations to generics to allow them to come on the market as well.

In other places and in this place I would expect our focus would be on the performance of those generics and not on the technology that was used to make that generic. So we would require that the generics demonstrate they are abuse-deterrent, the thing that we would all want to have rather than that they used the same technology. We think that would incentivize the development of appropriate generics, generics that work, while recognizing the important role that the innovator plays here in terms of developing new innovative products.[38]

In response to a subsequent question from Congressman Guthrie, Dr. Throckmorton summarized the status of the Agency's consideration of these questions as follows:

Q. [O]n Capitol Hill, there's been a lot of discussion about whether generic prescription opioids must have identical abuse-deterrent technology or whether it must simply be comparable or meet or exceed of the other drug. Can you discuss your perspective on this debate and what you are doing to ensure the process remains science-based and technology-neutral.

A. Absolutely and I think it is a very important question. We are going to be talking about – we are working internally on and we are planning on talking about it at a public meeting at the end of September and early October. What I anticipate is that we are going to rely on the generics demonstrating they are abuse-deterrent, not that they use the same technology. That would be the approach that we have used in other places.

And so the testing that we'll lay out, the testing that we will develop, will be to decide whether or not the new formulation, however it's made, is abuse-deterrent to the level that it needs to be compared with the innovator, not that it used the same technology.[39]

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38 *Id.* at pp. 57-58.

39 *Id.* at page 82.

At the September-October 2013 AD Science Meeting, Dr. Andre Raw, an OGD official, disclaiming that he was speaking for the Agency, shared his own views on the requirements for generic versions of OxyContin. In his presentation to the meeting, Dr. Raw indicated that generic versions of OxyContin should exhibit equivalent abuse-deterrent attributes, documented through testing against OxyContin where the results show no worse abuse-deterrent performance than that of OxyContin. The official further indicated that the particular studies that would be necessary to document this level of performance remain under discussion within the Agency, but that generic approval would be premised on performance based testing, not the use of particular technology.[40]

II. Argument

A. FDA May Not Approve A Proposed Generic Version Of An Abuse-Deterrent Product Which Has Not Been Shown To Have Equivalent Abuse-Deterrence

Dr. Throckmorton's testimony quoted above sets out the issue before the Agency in its consideration of proposed generic versions of an abuse-deterrent drug. Without requiring that a generic product use the same "technology" as the innovator, the generic would need to be proven to be abuse-deterrent "to the level that it needs to be compared with the innovator." Given the Agency's prior findings regarding abuse deterrence and the legal requirements for approval of generic drugs, "the level that it needs to be" can only refer to the generic being proven to be equally abuse-deterrent. It appears from comments by Dr. Raw and others at the AD Science Meeting that there may be wide agreement that generic versions of abuse deterrent products must establish abuse-deterrent attributes equivalent to the RLD.

Indeed, approval of a generic version of OxyContin that has not been shown to have equivalent abuse-deterrent attributes would be impermissible under Section 505(j) of the Act and the Administrative Procedure Act.[41] Proposed generic products that have not been shown, through the studies discussed in this Petition, to perform as well as reformulated OxyContin under conditions designed to simulate tampering do not have the same risk-benefit profile as reformulated OxyContin, are not as safe as reformulated OxyContin, and do not have the same performance characteristics as reformulated OxyContin. Simply put, such products cannot be considered to be "generic" equivalents

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[40] Remarks of Andre Raw, Ph.D, Director – Division of Chemistry 1, Office of Generic Drugs, Abuse Deterrence Science Meeting, September 30 – October 1, 2013, presentation available at: http://nebula.wsimg.com/5dff082634bb819fcb1a145f9209903b?AccessKeyId=7B2DBB1E2E28C2F11192&disposition=0. *See also* Remarks of Robert A. Rappaport, M.D. Director, Division of Anesthesia, Analgesia and Rheumatology Products Abuse Deterrence Science Meeting, September 30 – October 1, 2013.

[41] 5 U.S.C. § 706(2)(A).[42] *See generally* 21 U.S.C. § 355(j)(2)(A).

of reformulated OxyContin under the Hatch-Waxman Amendments. Any decision nevertheless to approve such a product as a generic version of OxyContin would be contrary to law and could not withstand review under the APA standards.

1. Generic Products Must Be As Safe And Effective As The Brand Name Drugs They Copy

The Hatch-Waxman Amendments of 1984 created an approval pathway for generic versions of approved innovator drug products, such as OxyContin. Through this approval pathway, a company seeking to market a generic copy of a previously-approved drug may file an ANDA, instead of an NDA. An ANDA filer is not required to duplicate the extensive preclinical and clinical data submitted by the innovator to establish safety and effectiveness of the Reference Listed Drug ("RLD") on which the ANDA relies. Instead, a generic applicant must include specified information designed to show that its generic product is the same as the RLD. With certain exceptions, these provisions require an ANDA to include information showing that the generic product has the same active ingredient, dosage form, dosage strength, route of administration, and labeling as the RLD, as well as information showing that the generic product is bioequivalent to the RLD.[42] Upon making the statutorily required showings, the generic applicant may piggyback on FDA's previous finding that the RLD is safe and effective, based on the extensive preclinical and clinical data submitted for the RLD.

The purpose of Section 505(j) "is to assure the marketing of generic drugs that are as safe and effective as their brand-name counterparts."[43] Almost twenty five years ago, FDA explained the Hatch-Waxman Amendments as follows:

> The ANDA provisions of Title I provide for approval of duplicate or related versions of approved drugs whose patents have expired, and that have been shown through the ANDA approval requirements to be as safe and effective as their brand name counterparts, but without the submission of duplicative safety and effectiveness data. Thus, these provisions are intended to encourage competition by decreasing the time and expense of bringing generic drugs to market, and thereby to provide the public with low cost drugs.[44]

FDA has implemented the Hatch-Waxman Amendments with this overarching purpose in

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42 *See generally* 21 U.S.C. § 355(j)(2)(A).

43 *Abbreviated New Drug Application Regulations; Proposed Rule,* 54 Fed. Reg. 28872, 28879 (July 10, 1989).

44 54 Fed. Reg. at 28874.

mind, adopting regulations that assure the marketing of generic drugs that are as safe and effective as their brand name counterparts.[45]

Courts also recognize that the Hatch-Waxman Amendments were designed to assure that generic drugs are as safe and effective as the brand name drugs they copy:

> The Hatch-Waxman Amendments permit the submission of an ANDA when an applicant can demonstrate that a generic drug meets stringent requirements designed to ensure that it is as safe and effective as the pioneer drug.[46]

FDA and other Federal agencies have routinely assured the public that generic drugs are as safe and effective as the innovator drugs they copy,[47] with the same risks and benefits as the branded drugs they copy:

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[45] *See, e.g.,* 54 Fed. Reg. at 28884; *see also Id.* at 28879; *Abbreviated New Drug Application Regulations* (Final Rule) 57 Fed. Reg. 17950, 17961 (April 28, 1992) (all discussing labeling regulations); 54 Fed. Reg. 28872, 28902 (discussing regulations concerning inactive ingredients); *see generally* Consolidated Response to Petitions, Docket Nos. 2001P-0323; 2002P-0447; and 2003P-0408 (Oct. 14, 2003) at p. 24 ("Because ANDAs are, by definition, for duplicates or minor variations of a reference listed drug and are, by definition, approved without submission of clinical or preclinical studies to establish safety or effectiveness they are statutorily presumed to have the same safety and effectiveness profile as the listed drug they reference").

[46] *Serono Labs, Inc. v. Shalala,* 974 F. Supp. 29, 31 (D.D.C. 1997); *see also Schering Corp. v. FDA,* 51 F.3d 390, 391, 396 (3d Cir. 1995) ("A bioequivalent generic drug is one that the FDA has determined to be as safe and effective as the pioneer drug it copies").

[47] *Understanding Generic Drugs,* available at: http://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/UnderstandingGenericDrugs/default.htm (generic drugs are "copies of brand-name drugs and are the same as those brand name drugs in dosage form, safety, strength, route of administration, quality, performance characteristics and intended use); *see also* What You Want to Know About Generic Drugs, Myths and Facts about Generic Drugs, at Myth # 1, available at: http://www.fda.gov/downloads/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/UnderstandingGenericDrugs/UCM169283.pdf (A generic drug is a "copy of a brand-name drug, which must have the same quality [and] same safety").

The Federal Trade Commission and the Center for Medicaid Services have also both assured the public that generic drugs are as safe and effective as the brand name drugs they copy. *See* Federal Trade Commission, Who Cares, Sources of Information about Health Care Products and Services (Oct. 2008), at p. 9, available at: http://www.ftc.gov/bcp/edu/pubs/consumer/health/hea17.pdf and FTC Facts for Consumers, Generic Drugs: Saving Money at the Pharmacy (May 1998), available at: http://www.ftc.gov/bcp/edu/pubs/consumer/health/hea06.pdf; Your Guide to Medicare Prescription Drug Coverage, CMS Product No. 11109 (March 2012), at p. 25, available at: http://www.medicare.gov/publications/pubs/pdf/11109.pdf (emphasis supplied). *See also* How Medicare Prescription Drug Plans and Medicare Advantage Plans with Prescription Drug Coverage (MA-PDs) Use

Are generic drugs as safe as brand-name drugs?

Yes. The FDA says that all drugs must work well and be safe. Generic drugs use the same active ingredients as brand-name drugs and work the same way. So they have the same risks and benefits as the brand-name drugs.[48]

2. Abuse Deterrence Is A Critical Safety Attribute That Must Be Duplicated By Proposed Generic Versions Of Abuse Deterrent Products

It is well recognized that abuse of prescription drugs results in serious adverse events, including death.[49] The White House has identified prescription drug abuse as an "epidemic" that is "the nation's fastest growing drug problem."[50] FDA has also recognized prescription drug abuse as a pressing public health problem, and has consistently encouraged development of products specifically formulated to deter abuse.[51]

Pharmacies, Formularies, and Common Coverage Rules, CMS Product No. 11136 (Feb. 2011), at p. 2, available at: http://www.medicare.gov/Publications/Pubs/pdf/11136.pdf

[48] Facts about Generic Drugs, available at: http://www.fda.gov/downloads/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/UnderstandingGenericDrugs/UCM219406.pdf (emphasis supplied); *see also* You know the questions that go through your mind when you take your generic drug? Here are the answers, DHHS Publication No. (FDA) 02-3243, available at: http://www.fda.gov/downloads/Drugs/EmergencyPreparedness/BioterrorismandDrugPreparedness/UCM133888.pdf (generic drugs "must meet the same quality and safety standards" as the brand name drugs they copy).

[49] 78 Fed. Reg. at 23274; Centers for Disease Control and Prevention; National Center for Injury Prevention and Control; Division of Unintentional Injury Prevention; Policy Impact: Prescription Painkiller Overdoses, available at: http://www.cdc.gov/homeandrecreationalsafety/rxbrief/; National Institute on Drug Abuse; Prescription Drugs: Abuse and Addiction (Oct. 2011), available at: http://www.drugabuse.gov/sites/default/files/rrprescription.pdf.

[50] Press Release, Office of National Drug Control Policy, Obama Administration Releases Action Plan to Address National Prescription Drug Abuse Epidemic; Announces FDA Action Requiring Drug Makers to Develop Education Program for Prescribers about Safe Use of Opioids (April 19, 2011), available at: http://www.whitehouse.gov/ondcp/news-releases-remarks/obama-administration-releases-action-plan.

[51] *See* Response to Citizen Petition, Docket FDA-2009-P-0227, at pp. 3, 6-7, available at: http://www.regulations.gov/#!documentDetail;D=FDA-2009-P-0227-0006; AD Guidance at p. 2; *FDA's Efforts to Address the Misuse and Abuse of Opioids*, available at: http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm337852.htm#drug_development.

Against this backdrop, FDA has recently confirmed – in its decision that the original formulation of OxyContin was withdrawn for reasons of safety, and that the original formulation of Opana ER was not – that abuse potential bears directly on a product's safety, and is considered in weighing a product's benefits and risks.[52] In the OxyContin decision, the Agency explained:

> FDA has long considered the abuse potential of a drug in numerous regulatory contexts. Where appropriate, FDA may take into account abuse potential as part of the safety profile of a drug when weighing its benefits and risks. In this case, FDA has considered the abuse potential as part of the Agency's determination of whether the original formulation of OxyContin was withdrawn from sale for reasons of safety or effectiveness. This approach is particularly appropriate here in light of the extensive and well-documented history of OxyContin abuse.[53]

These decisions, as well as similar historical actions,[54] which recognize attributes bearing on abuse as critical safety parameters, require that proposed generic versions of brand name products specifically formulated to discourage abuse and misuse be shown to have equivalent abuse-deterrent features. Only those generic products that actually duplicate the critical safety features of these innovative abuse-deterrent products can be considered to have the same risk-benefit profile.

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52 Opana ER Citizen Petition Response at p. 4; 78 Fed. Reg. at 23274.

53 78 Fed. Reg at 23274.

54 For example, over forty years ago, FDA withdrew approval under section 505(e) of all new drug applications for parenteral methamphetamine on the grounds that the products were unsafe due to the history of abuse of the products and the associated risk of dependence. *Opportunity for a Hearing on Proposal to Withdraw Approval of New Drug Applications,* 38 Fed. Reg. 4282 (Feb. 12, 1973); *Amphetamines for Human Use; Notice of Withdrawal of Approval of New Drug Applications,* 38 Fed. Reg. 8290 (March 30, 1973).

Similarly, decades ago, in connection with implementation of the DESI program, FDA stated that ANDAs were appropriate for products closely related to DESI drugs, but variations that pose significant questions of safety or effectiveness would not be eligible for approval via an ANDA. To illustrate the distinction, FDA explained that a controlled drug in a proposed dosage form that "offers or suggests an increased potential for abuse" raises such questions of safety or effectiveness rendering it ineligible for approval through an ANDA. *Abbreviated New Drug Applications, Proposed Related Drug Amendments,* 43 Fed. Reg. 39126, 39127 (Sept. 1, 1978); *Abbreviated New Drug Applications; Related Drug Amendments,* 48 Fed. Reg. 2751, 2753 (Jan. 21, 1983).

The Hatch-Waxman Amendments are intended to assure that generic drugs have the same risk-benefit profile and are duplicates of the brand name drugs they copy in terms of safety and performance characteristics. Consistent with this purpose, FDA has long assured healthcare practitioners and their patients that generic drugs are held to the same rigid standards as the brand name drugs they copy. The abuse-deterrent attributes of OxyContin are critical safety features, and therefore, the Hatch-Waxman provisions require that any generic copy be shown, through the comprehensive, comparative *in vitro* and *in vivo* testing discussed herein, to perform as well as OxyContin when subjected to known and anticipated methods of tampering and attempted abuse. Absent such data, there would be no basis to conclude that the proposed generic product has the same risk-benefit profile as OxyContin, was as safe as OxyContin, or performed the same as OxyContin. Approval of such a product would contradict the common and long-held understanding of what a generic drug is, and would be arbitrary and capricious.[55]

B. Proposed Generic Versions Of Reformulated OxyContin Must Be Comparably Abuse Deterrent In Order To Satisfy The "Same Labeling" Requirement

For any proposed generic version of OxyContin to meet the applicable generic labeling requirements, it must be shown through comprehensive, comparative *in vitro* and *in vivo* testing to perform as well as reformulated OxyContin under conditions designed to simulate tampering.

1. Generic Labeling Must Duplicate The "Abuse Deterrence Studies" Section Of OxyContin Labeling

In order to obtain ANDA approval, the labeling proposed for a generic drug must, with only limited exceptions, be the same as the labeling approved for the RLD. An ANDA that does not include information sufficient to show that the proposed labeling is the same as the labeling approved for the RLD is not approvable.[56] As discussed above, the labeling for OxyContin includes a section entitled, "Abuse Deterrence Studies" that describes the results of Purdue's drug-liking study and Purdue's *in vitro* manipulation studies. In the framework of FDA's January 2013 AD Guidance, the newly approved labeling statements are Tier 1 and Tier 3 claims. As specified in the AD Guidance, to

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[55] *See Motor Vehicle Mfr. Ass'n v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 43 (1983); *Teva Pharms., USA, Inc. v. FDA*, 182 F.3d 1003, 1011 (D.C. Cir. 1993) (FDA interpretation is arbitrary and capricious, in part because it produces absurd results contrary to the Hatch-Waxman Amendments); *Tummino et al. v. Hamburg*, __ F.Supp.2d __, 2013 U.S. Dist. LEXIS 49666 (E.D.N.Y. April 4, 2013) (FDA decision is arbitrary and capricious, in part due to departures from established agency policies and practices).

[56] 21 U.S.C. §§ 355(j)(2)(A)(v); 355(j)(4)(G); *see also* 21 C.F.R. § 314.127(a)(7).

assure that label text is not misleading and is based on as a complete and scientifically rigorous understanding as possible, a sponsor generally must provide data from Categories 1, 2, and 3 studies, *i.e., in vitro,* pharmacokinetic, and abuse-potential studies, in order to include Tier 1 and Tier 3 claims in product labeling. Therefore, these types of studies would be required of any applicant seeking approval of Tier 1 and Tier 3 claims, including a generic applicant. In addition, including the "Abuse Deterrence Studies" text in the label of a generic product would be misleading, and would misbrand the generic product,[57] unless the ANDA contained data demonstrating that the generic product has abuse-deterrent properties equivalent to those of OxyContin. Accordingly, FDA may not approve an ANDA referencing OxyContin unless the applicant establishes (by data demonstrating that the proposed generic formulation has abuse-deterrent properties at least as robust as those of OxyContin) that its formulation accurately duplicates the description in the abuse-deterrence section of the OxyContin labeling.

2. The Limited Exceptions to the Same Labeling Requirement Do Not Apply

The "same labeling" requirements of Section 505(j) do not permit generic versions of OxyContin to omit the "Abuse Deterrence Studies" section of the OxyContin labeling. FDA has repeatedly emphasized that "the exceptions to the requirement of 'same labeling' are limited,"[58] and neither of the two categories of recognized exceptions allows omission of the "Abuse Deterrence Studies" section of the OxyContin label.

First, generic labeling may differ from that of the RLD because the products are produced or distributed by different manufacturers. This exception permits only minor differences in labeling that do not reflect any diminution in safety or effectiveness, such as different expiration dates, addresses, inactive ingredients, or NDC numbers.[59] It has never been used to justify omission of lengthy text describing safety features that are not

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[57] 21 U.S.C. § 352(a).

[58] 54 Fed. Reg. at 28879, 28884; *see also id.* at 28881 ("Consistent labeling for duplicate versions of a drug product, insofar as this is possible, will avoid differences that might confuse health care professionals who prescribe and dispense prescription drug products or might create omissions of significant information").

[59] 21 C.F.R. §§ 314.94(a)(8)(iv), 314.127(a)(7); 54 Fed. Reg. at 28884. The legislative history to the Hatch-Waxman Act confirms that label differences permitted because of a difference in manufacturer are limited. The House Report on the 1984 Amendments described the intent of Congress: "The Committee recognizes that the proposed labeling for the generic drug may not be exactly the same. For example, the name and address of the manufacturers would vary as might the expiration dates for the two products. Another example is that one color is used in the coating of the listed drug and another color is used in that of the generic drug." *See* H.R. Rep. No. 857, Part I, 98th Cong., 2d Sess., at 22. These examples mentioned by Congress illustrate the type of non-substantive differences between generic and RLD labeling that are permissible.

present in the proposed generic product. In addition, labeling protected by patent or exclusivity may be omitted, but only if the applicant demonstrates that the differences in labeling do not render the proposed generic product less safe or effective than the RLD for the remaining, non-protected conditions of use.[60]

Because FDA has recognized that the abuse-deterrent features of OxyContin contribute significantly to the safety profile of the product, neither exception permits omission of the Abuse Deterrence Studies section of the OxyContin labeling from the labeling of a proposed generic product that lacks an equivalent level of abuse deterrence.

3. Generic Labeling May Not Lawfully Include The Enhanced Warnings Or Other Differences That Would Be Necessary, Were the Product Not Shown To Have Equivalent Abuse Deterrent Features

Were FDA to consider approving a proposed generic product that had not been shown to be as abuse deterrent as OxyContin, it would then be necessary for the generic label to include significant additional safety related labeling to alert healthcare practitioners to the differences between the generic product and reformulated OxyContin. However, the narrow exceptions to the "same labeling" requirement do not authorize the addition of warnings, precautions or other text to generic labeling intended to address safety concerns not applicable to the reference listed drug. In the words of FDA:

> FDA emphasizes that the exceptions to the requirement that a generic drug's labeling be the same as that of the listed drug are limited. The agency will not accept ANDA's for products with significant changes in labeling (such as new warnings or precautions) intended to address newly introduced safety or effectiveness problems not presented by the listed drug. Such labeling changes do not fall within the limited exceptions in sections 505(j)(2)(A)(v) and 505(j)(3)(G) of the act. Moreover, FDA does not believe that it would be consistent with the purpose of section 505(j) of the act, which is to assure the marketing of generic drugs that are as safe and effective as their brand-name counterparts, to interpret section 505(j)(2)(A)(v) of the act as permitting the marketing of generic drugs with diminished safety or effectiveness and concomitantly heightened labeled warnings. Thus, where a proposed change in a generic drug, e.g., in packaging or inactive ingredients or, for a petition-approved change, would jeopardize the safe or effective use of the product so as to necessitate the addition of significant new labeled warnings, the proposed product would

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[60] 21 C.F.R. §§ 314.94(a)(8)(iv), 314.127(a)(7).

not satisfy the labeling requirements of sections 505(j)(2)(A)(v) and [505(j)(4)(G)].[61]

A generic product that did not have equivalent physicochemical safeguards would need explicitly to describe those differences in properties and include heightened warnings describing the abuse and misuse situations in which the ANDA product is not expected to perform as well as reformulated OxyContin. Depending on the attributes of the generic product, it also may be necessary to include labeling describing the patient population (if any) for whom it is appropriate to prescribe a product that lacks the physicochemical safeguards provided by OxyContin.[62]

As Dr. Cone explains in his 2012 Declaration:

> In my view, if FDA determined to approve a generic product that did not have at least the same safety-related physicochemical properties as reformulated OxyContin, it would be absolutely essential to include explicit labeling describing those differences in properties and heightened warnings describing the abuse and misuse situations in which the product is not expected to perform comparably to OxyContin. However, the need for such warnings in that hypothetical situation simply reinforces my point – that a non-tamper resistant version of OxyContin would represent an increased public health and safety risk to patients and to the community and should not be allowed.

Exhibit A-2, ¶ 12, note 5.[63]

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[61] 54 Fed. Reg. at 28884.

[62] This type of information would be required in the 'Warnings and Precautions' and the 'Highlights' sections of the generic label. FDA regulations require the Warnings and Precautions section of the package insert to include "clinically significant adverse reactions," "other potential safety hazards," "limitations in use imposed by them," and "steps that should be taken if they occur." 21 C.F.R. § 201.57(c)(6). The Warnings and Precautions subsection of the Highlights section of the label must include, "A concise summary of the most clinically significant information required [in the Warnings and Precautions section of the package insert] . . . including information that would affect decisions about whether to prescribe a drug, recommendations for patient monitoring that are critical to safe use of the drug, and measures that can be taken to prevent or mitigate harm." 21 C.F.R. § 201.57(a)(10).

[63] In addition, to ensure that any differences between OxyContin and a generic product were understood by relevant healthcare practitioners and patients, and any related limits on distribution were adhered to, the generic product would also require a different Risk Evaluation and Mitigation Strategy ("REMS") than the one in place for OxyContin. Absent such an enhanced REMS, including additional educational materials describing the differences in safety-related physicochemical properties between the generic product and OxyContin, and potentially also including distribution limitations, the risks posed by the generic product would necessarily outweigh the benefits. However, the FFDCA does not permit

In sum, only those proposed generic products that have been shown to have equivalent abuse-deterrent features through the *in vitro* and *in vivo* testing described in this Petition could duplicate the "Abuse Deterrence Studies" section of OxyContin labeling. In the context of a generic product that is not subjected to the testing described in this Petition, there would be no basis to conclude that the generic product has the same abuse-deterrent properties as OxyContin or is as safe as OxyContin. In the case of a generic product that is tested, but fails to meet the specified acceptance criteria, available evidence would indicate that the generic product is not comparably abuse deterrent and is not as safe as OxyContin. In either situation, labeling could not be approved for the product, given the significant label omissions and clear label warnings that would be necessary, precluding a finding that the labeling is the "same" as that of OxyContin.

C. FDA's Legal Authority To Require Generic Versions of Reformulated OxyContin To Demonstrate Equivalent Abuse Deterrence Extends Beyond the "Same-Labeling" Requirements

As part of its mission to protect and promote the public health, FDA is charged with ensuring the safety and efficacy of the drug supply.[64] While Congress created an abbreviated approval pathway for generic products, the pathway was carefully circumscribed by statutory provisions providing for FDA review of various types of information that would assure that a generic performs the same, has the same quality, and is equally safe and effective, as the brand name drug it duplicates. In the context of reformulated OxyContin, this requires a showing that proposed generic copies perform as well as reformulated OxyContin when tested in experiments intended to simulate attempted tampering by potential abusers or by patient/caregivers inadvertently misusing the medication.[65] The authority to require applicants seeking to market generic versions of OxyContin to show equivalence under the *in vitro* and *in vivo* test conditions discussed in this Petition extends beyond that provided under the "same-labeling" standard described above and includes at least the following three additional statutory authorities:

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differences among brand and generic REMS (21 U.S.C. § 355-1(i)), providing another reason for FDA to refuse to approve such a product.

[64] *See* Strategic Priorities, 2011-2015, Responding to the Public Health Challenges of the 21st Century, Department of Health and Human Services, United States Food and Drug Administration, available at: http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UCM252092.pdf; Strategic Plan for Risk Communication, Fall, 2009, available at: http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/ucm183673.htm.

[65] A recent court decision confirms that FDA has broad authority to request various types of data necessary to make the findings required to approve an ANDA listed in 21 U.S.C. § 355(j)(4) and is not limited to the types of data specifically mentioned in 21 U.S.C. § 355(j)(2)(A). *See Sanofi-Aventis U.S. LLC v. FDA*, 842 F. Supp. 2d 195, at 202-210 (D.D.C. 2012).

- **Same Dosage Form:** FDA may not approve an ANDA if information submitted in the application is insufficient to show that the dosage form of the proposed generic product is the same as that of the listed drug. 21 U.S.C. § 355(j)(4)(D); 21 C.F.R. § 314.127(a)(4). *See* August 28, 2012 Petition at pp. 50-57.[66]

- **Bioequivalence:** An ANDA is not approvable absent data showing that the proposed generic product is bioequivalent to the RLD on which the ANDA relies. 21 U.S.C. §§ 355(j)(2)(A)(iv), 355(j)(4)(F); 21 C.F.R. §§ 314.94(a)(7), 314.127(a)(6). *See* August 28, 2012 Petition at pp. 57-59.

- **Inactive ingredients/Composition of Drug Product:** An ANDA must "identify and characterize the inactive ingredients in the proposed drug product and provide information demonstrating that such inactive ingredients do not affect the safety or efficacy of the proposed drug product." 21 C.F.R. § 314.94(a)(9)(ii). FDA may not approve an ANDA if information shows that the inactive ingredients of the drug are unsafe for use under the conditions prescribed, recommended, or suggested in the labeling proposed for the drug, or the composition of the drug is unsafe under such conditions because of the type or quantity of inactive ingredients included or the manner in which the inactive ingredients are included. 21 U.S.C. § 355(j)(4)(H) ; 21 C.F.R. § 314.127(a)(8)(i). *See* August 28, 2012 Petition at pp. 62-67.

D. To be Considered a Generic Equivalent to Reformulated OxyContin, a Proposed Generic Product Must Be Shown To Be Equivalent On Each Recommended Test

For a proposed generic product to be as safe as reformulated OxyContin and to comply with the generic drug approval standards of Section 505(j), it is essential that the product be as abuse-deterrent as reformulated OxyContin. *In vitro* and *in vivo* test data predicted that the physicochemical attributes of reformulated OxyContin would impact the safe use of the product by deterring would-be abusers and patients who might otherwise inadvertently misuse the product. Epidemiologic data continue to confirm the validity of that prediction. However, there is no basis to conclude that any particular ingredient, method of manufacture, or abuse-deterrent feature of OxyContin is solely or primarily responsible for the observed ability of the product to deter misuse and abuse. Similarly, no data indicate that the observed benefits of the physicochemical properties of reformulated OxyContin could be preserved were any one or more of the product's abuse-deterrent features omitted. Rather, as discussed in the attached declaration of Dr.

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[66] These statutory and regulatory provisions were discussed at length in Purdue's previous petitions: the Citizen Petition dated July 13, 2012, Docket No. FDA-2012-P-0760, refiled with non-substantive changes on August 28, 2012, Docket No. FDA-2012-P-939. Relevant passages from these prior petitions are cross referenced for convenience.

Cone, the abuse-deterrent attributes of reformulated OxyContin tablets are "cumulatively critical to the successful deterrent effect of the product. Each feature adds to the time and effort needed to prepare the tablets for abuse and reduces the ability of abusers to achieve the reinforcing effects they seek by various routes of administration."[67]

For this reason, equivalent abuse deterrence can only be documented though comparative testing designed to evaluate equivalence on each critical abuse-deterrent feature of reformulated OxyContin. A less comprehensive testing strategy could lead to approval of a "generic" product which, even if formulated to have abuse deterrent features, is uniquely vulnerable to one or more particular manipulations – a fact that would quickly become widely known among the population of abusers.[68] As reflected in the Agency's decision on Opana ER, such vulnerabilities may be present even in a formulation that is in some respects similar to that of reformulated OxyContin. As described by the sponsor of Opana ER in its submission to the Agency, the reformulated versions of both OxyContin and Opana ER "contain the exact same inactive polymer that imparts abuse-deterrent physicochemical properties to both tablets. This polymer imparts to both products the crush-resistant properties that abusers find extremely difficult to overcome." Based on the similarity in formulations, physicochemical properties, and other factors, the sponsor argued that both products have "virtually identical abuse-deterrent properties."[69] However, despite these similarities, after careful review of the data, FDA rejected the sponsor's argument that the abuse-deterrent properties of reformulated Opana ER and reformulated OxyContin are virtually identical, and therefore warranted the same regulatory determinations. By way of example, the Agency explained that reformulated OxyContin has physicochemical properties expected to make abuse by injection difficult, while Opana ER "can be readily prepared for injection."[70] In the case of generic products, similarly careful scrutiny of the abuse deterrent properties of

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67 Appendix A, ¶ 13.

68 Appendix A, ¶ 14.

69 *See* April 23, 2013 submission by Endo Pharmaceuticals Inc. to FDA-2012-P-0895, at pp. 2, 3, 6-8, available at: http://www.regulations.gov/#!documentDetail;D=FDA-2012-P-0895-0012.

70 Opana ER Citizen Petition Response at p. 8. Similarly, Acura Pharmaceuticals recently announced that a product formulated with the company's abuse deterrent AVERSION technology did not achieve statistical significance on the primary endpoint in a Phase II clinical abuse liability study, and that the results were, in certain respects, inconsistent with results from a similar study conducted on another, already approved, tablet product formulated with Acura's abuse deterrent AVERSION technology. *See* Acura Pharmaceuticals Announces Top-Line Results of a Clinical Study Assessing Abuse Liability (Aug. 26, 2013), available at: http://investors.acurapharm.com/releases.cfm. This and the Opana ER example both illustrate the importance of comprehensive testing to evaluate abuse-deterrent properties, rather than more limited testing and reliance on similarities in formulations.

the formulation is necessary. Nothing about the robustness of the purported abuse-deterrent properties of a product can be inferred solely from its formulation.

In order to show equivalent safety to OxyContin, proposed generic copies must be evaluated, and pass, at least the specific tests/test batteries outlined by Dr. Cone. All tests should include, as controls, reformulated OxyContin and powdered oxycodone API. Test results of the generic product should be equivalent (or better) than OxyContin, and in no cases should the generic product demonstrate less robust abuse-deterrent properties. This should be established through statistical analyses which support the conclusion that the proposed generic product is at least as resistant as reformulated OxyContin to the respective tested methods of product manipulation.[71]

As suggested at the AD Science Meeting, FDA and generic applicants may consider the possibility of generating post-approval epidemiologic data to assess potential differences between the real-world abuse and misuse of generic extended-release oxycodone and of OxyContin. An applicant's willingness to conduct post-marketing epidemiologic studies or other studies of a generic drug, however, cannot substitute for rigorous premarket testing documenting that the proposed generic product is equivalent to the RLD, including that it has abuse-deterrent properties as robust as the RLD. In the case of proposed generic versions of OxyContin, such test documentation must include, at a minimum, passing each of the tests/test batteries discussed below. The Hatch-Waxman generic approval criteria do not permit reliance on post-approval commitments to justify approval of a generic drug which the sponsor has not proven to be equivalent to the RLD.

The premarket tests/test batteries, and the rationale for each, are described by Dr. Cone in paragraph 15 of his declaration as follows:

(a) **Tablet/pill manipulation studies** to establish that it is at least as difficult and time-consuming to compromise the integrity of the proposed generic tablets and to reduce them to fine particles as it is to do so with reformulated OxyContin. The studies should assess the relative difficulty of reducing the tablets to fine powders using a variety of commonly available tools. The range of tools employed in these studies should include crushing between two spoons, hammer, mortar and pestle, cutting with knives, graters, and with coffee grinders. Both the amount of time and effort necessary, and the resulting particle size distribution of the test product and the OxyContin control, resulting from use of each tool should also be assessed and reported. *See* AD Guidance at p. 4.

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[71] Appendix A, ¶¶ 17, 14-15.

These studies are necessary to assure that the generic product has the same baseline level of abuse-deterrence that flows from the impediments to physical manipulation of the reformulated OxyContin tablets. The ability to more easily or more quickly reduce a proposed generic product to fine particles using any common tool, compared to reformulated OxyContin, will represent a unique vulnerability of the generic product to abuse and misuse. Even if the generic product has other attributes which meet or exceed the protective characteristics of reformulated OxyContin, the absence of this baseline level of deterrence would mean that the generic product would rely to an inordinate extent on its other characteristics to achieve abuse-deterrence – precluding a meaningful prediction of the overall comparability of the abuse-deterrence features of the generic to reformulated OxyContin.

(b) ***In vitro* small and large volume extraction and dissolution studies** on intact tablets and on standardized particle sizes of manipulated tablets, using an appropriate range of solvents, conditions, and pretreatments. The range of solvents should include water, alcohol, simulated gastric fluid, as well as other solvents with a range of chemical properties (*e.g.*, a range of pH, different polarity, and protic and aprotic solvents). The selection of solvents should take into account knowledge of the constituents of the proposed generic formulation for the purpose of comprehensively assessing any potential unique vulnerabilities of the product associated with its formulation. Conditions tested should include a range of temperatures, times, and stirring/agitation settings. Study conditions should be sufficiently aggressive to take the formulation to a state of no further change or to failure (near complete API isolation). Pretreated product (intact tablets and standardized particle sizes of manipulated tablets) should also be tested under the same range of conditions. Pretreatments that should be evaluated include freezing, various dry heat baking conditions (heating time, temperature) and various microwave conditions (microwave times). These pretreated products should be tested by further physical manipulations, extraction tests, dissolution tests, syringeability tests, and smoke-ability tests to determine if the deterrent features of the formulation are compromised or defeated. *See* AD Guidance at p. 4.

These studies simulate the range of extraction and dissolution techniques which abusers commonly use in an attempt to defeat controlled-release mechanisms and to extract pure, immediately available drug from a tablet dosage form. These efforts are directed at preparing the drug for oral ingestion, for intranasal insufflation, for injection, or as a precursor to further manipulations or purification of the drug for various routes and methods of administration. The ability to more easily extract the oxycodone from a generic tablet than from reformulated OxyContin would create a unique vulnerability, potentially leading to multiple unique opportunities and incentives to seek out the generic product for abuse.

(c) ***In vitro* studies measuring the syringability and injectability of tablet contents**, extracted by standardized procedures. The procedures should include extraction of standardized fine particles of the proposed tablet formulation and of OxyContin, at room temperature and at near boiling conditions in 1, 2, 5, and 10 mL of water and saline. Syringeability testing should be performed on the resulting solution by attempting to draw the resulting liquid into a syringe fitted with needles of different sizes (18 gauge to 28 gauge). Injectability testing should be performed on the resulting solution by loading the syringe barrel with the solution, inserting the syringe plunger and attempting to expel solution through needles of different sizes (18 gauge to 28 gauge). As noted above, these tests should also be conducted on pretreated fine particles of the formulation. *See* AD Guidance at p. 5.

These studies measure the ability to prepare a tablet dosage form for injection by extracting the drug into a small-volume of liquid. If the resulting liquid contains oxycodone and can be drawn through a syringe or expelled from a syringe, that would represent a significant vulnerability of the formulation compared to reformulated OxyContin, which cannot be prepared for injection in this way.

(d) ***In vitro* studies measuring the ability to create and isolate free oxycodone base** from the tablets. This test will evaluate the risk that sophisticated abusers would be able, through commonly known techniques of reducing a salt to its free base, to isolate free oxycodone base from the proposed generic tablets. *See* AD Guidance at p. 4. Given that such procedures are understood by industry and that detailing them here in a public document may create a "roadmap" for abusers, Purdue and Dr. Cone do not believe it appropriate to describe them in a publicly available petition. Dr. Cone is prepared to describe those procedures to FDA, if requested, in a non-public setting.

These studies assess the vulnerability of the tablets to techniques commonly used to isolate and convert the oxycodone hydrochloride content of the tablets into a free base form of oxycodone – an approach potentially suitable for isolating a vaporizable (inhalable) or injectable form of the drug. Reformulated OxyContin impedes efforts to isolate free base of oxycodone from the tablets. If a proposed generic formulation does not impede such extraction techniques, Dr. Cone expects that fact will become quickly known to the abuser community, resulting in a unique and serious vulnerability for the generic product.

(e) ***In vitro* vaporization studies** simulating drug smoking. These laboratory studies measure the ability to vaporize oxycodone from fine particles prepared from the tablets by heating the fine particles in a controlled laboratory environment in which the resulting vapor and residue is collected and analyzed for oxycodone content. *See* AD Guidance at p. 4.

These studies, conducted using standardized laboratory equipment, assess the degree to which the tablet formulation impedes effective vaporization of the drug into a form suitable for abuse by inhalation. Vulnerability of a generic formulation to abuse by vaporization and inhalation would be a unique risk enabling administration via a highly reinforcing route.

(f) **An *in vivo* bioequivalence study with clinical endpoints evaluating the relative abuse potential of orally ingested crushed/manipulated tablets.** This study would measure the degree to which the extended release mechanism of the proposed product is preserved upon oral ingestion of chewed tablets and fine or coarse particles prepared from the tablets, assessing comparative equivalence to similar preparations of OxyContin in blood-level measurements of T_{max}, C_{max}, and AUC. *See* AD Guidance at p. 6. In order to assess the relative impact of the formulations on the overall desirability of this route of administration, standard "liking" assessments should also be conducted and compared.[72] As specified in the AD Guidance, these tests should be randomized, double-blind, placebo (as well as active-comparator, *i.e.,* OxyContin and oxycodone API) controlled cross over studies in a non-physically dependent population of opioid-experienced abusers with a history of oral abuse, which has been pre-qualified to ensure that they can distinguish between the treatments. *See* AD Guidance at pp. 6, 7-13.

Drug Liking Visual Analogue Scale ("VAS"), Good Effects VAS, Bad Effects VAS, and Any Effects VAS should be assessed periodically following administration, with pharmacokinetic measurements taken at the same time points. Overall Drug Liking VAS, and Take Drug Again VAS should be assessed several hours after administration. Maximum peak effect (E_{max}) of drug liking VAS and time to maximum peak effect (TE_{max}) should be compared.

The procedures for preparing fine and coarse particles of OxyContin and the generic product must be standardized, and the resulting particle size distributions documented. Standardized instructions designed to achieve consistent, rapid and complete administration of study drug should be provided to subjects, including instructions designed to minimize variability in those portions of the test involving the chewing of tablets by the study subjects themselves.

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[72] For a description of standard liking assessments, *see* Walsh, S.L., *et al.,* 2008. *The relative abuse liability of oral oxycodone, hydrocodone and hydromorphone assessed in prescription opioid abusers.* Drug Alcohol Depend. 98, 191-202, attached as Exhibit A-3. *See also Guidance for Industry, Assessment of Abuse Potential of Drugs* (Draft) (Jan. 2010) at p. 15, available at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm334743.pdf.

This study will assess the degree to which the abuse-deterrence features of the tablets limit the clinical effect of ingesting the manipulated tablets, including the degree to which users report "liking" the experience – an assessment which can only be made in a realistic clinical use simulation. It is not possible to predict, solely from *in vitro* studies, whether a proposed generic formulation will perform as well as reformulated OxyContin in this multifaceted clinical context.[73] If the generic product is significantly more reinforcing (*i.e.*, "liked") than reformulated OxyContin in these tests, that vulnerability can be expected to become well known and to cause significant demand for the generic product. For this reason, the analysis of the "liking" measures in this study should establish "non-inferiority" instead of the standard statistical measures of bioequivalence. This is because a test product which is less effective than OxyContin in reducing liking would be more vulnerable to abuse and should not be approved, but there is no reason to reject a test product which proves more effective in reducing liking.[74]

(g) **An *in vivo* bioequivalence study with clinical endpoints evaluating the relative abuse potential of insufflated fine particles** of the generic and OxyContin tablets. *See generally* AD Guidance at pp. 6, 7-13. In this study, blood level measures of T_{max}, C_{max}, and AUC should be compared. In order to assess the relative impact of the formulations on the overall desirability of this route of administration, standard "liking" assessments should also be conducted and compared.[75] As with the studies of orally ingested tablets described in section (f) above, these tests should be randomized, double-blind, placebo (as well as active-comparator, *i.e.*, OxyContin and oxycodone API) controlled cross over studies.

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[73] I note that presenters at the recent Abuse Deterrent Formulation Science Meeting made this same point. *See, e.g.*, The Role and Interpretation of Pharmacokinetic Parameters in Assessment of Abuse Liability: Category 2 Studies, Sharon L. Walsh, Ph.D., available at: http://nebula.wsimg.com/d69522176ba8a1ad9e8fb242967dd324?AccessKeyId=7B2DBB1E2E28C2F11192&disposition=0 and PK/PD analysis in assessment of abuse deterrence, Megan J. Shram, Ph.D, available at: http://nebula.wsimg.com/b7b10689b87f5e7cd6fadc494382eb1c?AccessKeyId=7B2DBB1E2E28C2F11192&disposition=0.

[74] Assessments of the relative liking of a proposed generic product and OxyContin when ingested and when insufflated (*see* section (g) below) are particularly important because epidemiologic data indicate lower rates of abuse of reformulated OxyContin via both of these common routes of administration, compared to abuse of the original formulation of OxyContin. *See, e.g.*, Appendix C, Section II (discussing the results of the NAVIPPRO study). While Purdue's clinical studies evaluating oral administration of manipulated reformulated OxyContin did not include assessments of drug liking, Purdue's subsequent clinical development programs for abuse-deterrent extended-release opioid formulations, developed in consultation with the FDA, include PK/PD studies evaluating drug liking following oral administration.

[75] *See* note 72 above.

The study should be conducted in a non-physically dependent population of opioid-experienced abusers with a history of intranasal abuse, which has been pre-qualified to ensure that they can distinguish between the treatments.

Drug Liking Visual Analogue Scale ("VAS"), Good Effects VAS, Bad Effects VAS, and Any Effects VAS should be assessed periodically following administration, with pharmacokinetic measurements taken at the same time points. Overall Drug Liking VAS, and Take Drug Again VAS should be assessed several hours after administration. Maximum peak effect (E_{max}) of drug liking VAS and time to maximum peak effect (TE_{max}) should be compared. Measures should also be employed that assess the specific occurrence of nasal irritation or other nasal problems noted by the study subjects.

The procedures for preparing fine and coarse particles of OxyContin and the generic product must be standardized, and the resulting particle size distributions documented. Standardized instructions designed to achieve rapid and complete administration of study drug should be provided to subjects.

This study will assess the degree to which the abuse-deterrence features of the tablets limit the clinical effect of insufflation of the manipulated tablets, including the degree to which users report "liking" the experience – an assessment which can only be made in a realistic clinical simulation of real world abuse. *In vivo* studies of reformulated OxyContin, compared to original OxyContin, showed significant decrease in the degree of absorption of oxycodone from the reformulated version of the drug, and a significant reduction in drug liking, as is now reflected in Section 9.2 of the OxyContin labeling. It is not possible to predict, solely from *in vitro* studies and pharmacokinetic studies, whether a proposed generic formulation will perform as well as reformulated OxyContin in this multifaceted clinical context, where multiple aspects of drug administration and effect bear on the overall experience of the subject. If the generic product is significantly more reinforcing (*i.e.*, "liked") than reformulated OxyContin in these tests, that vulnerability can be expected to become well known and to cause significant demand for the generic product. For this reason, the analysis of the "liking" measures in this study should establish "non-inferiority" instead of the standard statistical measures of bioequivalence. This is because a test product which is less effective than OxyContin in reducing liking would be more vulnerable to abuse and should not be approved, but there is no reason to reject a test product which proves more effective in reducing liking.

(h) Finally, generic manufacturers must also give careful additional consideration to any physical and chemical features of the proposed generic product which differ from those of reformulated OxyContin. Any potential formulation-specific vulnerabilities associated with physical and chemical features of the generic

product must be explored through additional comprehensive *in vitro* and/or *in vivo* testing, as appropriate, using reformulated OxyContin as a control.

Consistent with the studies conducted on reformulated OxyContin and the methodology discussed in the Agency's January 2013 draft AD Guidance, these studies must be conducted in a scientifically rigorous manner, incorporating key elements intended to assure the reliability and validity of the data: testing of all dose strengths; use of sufficient replicates for evaluation of method variability; inclusion of adequate controls and comparators for comparison of results; investigation over a wide range of chemical and physical conditions; experimentation over adequate time periods to determine failure limits; verification of analytical methods; and use of independent laboratories to whom methodologies have been transferred.[76]

E. An Extended-Release Oxycodone Product That Cannot Pass Each Of The Tests Discussed In This Petition May Be Evaluated Only Under Section 505(b) Of The Act

A company seeking to market a new drug product must file either an NDA under Section 505(b) of the Act, or an ANDA under Section 505(j) of the Act. As discussed above, an extended-release oxycodone product that cannot be shown to have abuse-deterrent features equivalent to those of OxyContin is not eligible for approval under Section 505(j) because it is not as safe as OxyContin and cannot duplicate the "Abuse Deterrence Studies" section of the OxyContin labeling. Such products must be approved, if at all, under Section 505(b) of the Act. Presumably, applications for abuse-deterrent extended-release oxycodone drug products would rely, to some extent, on FDA's previous findings of safety and efficacy for OxyContin, and would therefore be submitted as 505(b)(2) applications. Such applications would also include data establishing that the changes from OxyContin also satisfy FDA's safety and effectiveness standards.[77]

Products that are ineligible for approval through the ANDA process include those that incorporate some form of physical/chemical barriers to abuse like OxyContin, but

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[76] Appendix A, ¶ 16.

[77] *See generally,* Consolidated Response to Petitions, Docket Nos. 2001P-0323; 2002P-0447; and 2003P-0408 (Oct. 14, 2003) at p. 15 (A 505(b)(2) applicant may "rely on the fact that FDA found a drug product with certain characteristics to be safe and effective," and to "target its studies to prove how changes from this previously approved drug product also meet the FDA's safety and effectiveness standards"); Response to Petitions, Docket Nos. FDA-2007-P-0128; FDA-2009-P-0040 (July 29, 2009) at p. 4 ("A 505(b)(2) application that relies on the finding of safety or effectiveness for a listed drug must bridge to the listed drug it references and support any differences from the listed drug it references with appropriate safety and effectiveness information"); 21 C.F.R. § 314.54(a).

nevertheless fail one or more of the tests discussed in Section D above.[78] In this case, failure of one or more of those tests establishes that the product has a unique vulnerability not applicable to OxyContin, and is therefore not as safe as OxyContin. Differences such as this, which have "significant therapeutic implications or otherwise require additional clinical studies to establish safety," necessarily preclude ANDA approval.[79] The decision whether to approve such a product entails an exercise of judgment based on the significance of the failure(s), any data indicating the product has additional abuse-deterrent features not present in OxyContin, and an overall assessment of the risk/benefit profile of the product. These type of assessments are outside of the scope of the 505(j) approval criteria, but are routinely made in the context of an NDA, including a 505(b)(2) application.[80]

In contrast, a product using different technology to impart physical/chemical barriers to abuse, but that is shown, through the tests described in Section D above, to have equivalent abuse-deterrent properties, is eligible for review and approval under Section 505(j). The critical question is whether the proposed product is proven to have abuse-deterrent features equivalent to those of OxyContin–not whether the products employ the same or similar technology to achieve the pertinent physical/chemical barriers to abuse.

Just as generic applicants may employ alternate controlled-release mechanisms to achieve an equivalent bioavailability profile, proposed generic versions of OxyContin may use any inactive ingredients and formulation/manufacturing techniques that result in a tablet with demonstrably equivalent physical/chemical barriers to abuse. However, bio-inequivalent products cannot be approved under Section 505(j) as generics even if they are supported by evidence that they might nevertheless be safe and effective.[81] Similarly, FDA has found that an ANDA for a drug administered via an auto-injector must include extensive comparative performance testing and other data establishing that the auto-

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[78] As discussed in Section I.C. above, the Draft AD Guidance sets forth six categories of abuse-deterrent formulations. Reformulated OxyContin falls into the "physical/chemical barriers" category.

[79] Response to Petitions, Docket Nos. FDA-2007-P-0128; FDA-2009-P-0040 (July 29, 2009) at p. 4 ("Where products with the same active ingredient, strength, dosage form, and route of administration have differences in packaging configurations, inactive ingredients, or other differences that have significant therapeutic implications or otherwise require additional clinical studies to establish safety and effectiveness, however, the products will not meet the standards for ANDA approval").

[80] *See generally,* Managing the Risks from Medical Product Use: Creating a Risk Management Framework, *What is FDA's Role in Minimizing Risks?*, available at: http://www.fda.gov/Safety/SafetyofSpecificProducts/ucm180542.htm .

[81] *See* Response to Citizen Petition and Petition for Stay of Action, Docket No. 93P-0421 (Aug. 12, 1997), at pp. 11-14.

injector constituent is equivalent to that of the RLD in terms of performance characteristics, operating principles, and critical design attributes. FDA does not require that all design features of the auto-injector be identical to the RLD, and instead allows design differences that do not significantly alter product performance or operating principles, and do not result in impermissible differences in labeling. However, if FDA determines that the auto-injector constituent of a proposed generic product is not equivalent to the auto-injector constituent of the RLD in terms of performance and critical design, FDA will refuse to approve the ANDA for that product, and it must be reviewed under Section 505(b).[82]

Also ineligible for approval under the ANDA process are those products that fall within the different categories of abuse-deterrent formulations specified in the AD Guidance, such as agonist/antagonist combinations or products containing aversive agents. These products, because of their fundamentally different approach to the problem of abuse, would necessarily fail several of the tests discussed in Section D above, and would necessitate different labeling than that approved for OxyContin, even if their abuse-deterrent features were demonstrated to be robust. The only means to evaluate whether such products offer equivalent abuse deterrence and are as safe as OxyContin would be through postmarketing studies comparing the real world impact of both formulations. In the necessary absence of such data before approval, however, the decision whether to approve such a product entails an exercise of judgment and an overall assessment of the risk/benefit profile of the product, taking into account data evaluating the abuse-deterrent features of the product and the expected significance of those features. As noted above, these types of assessments cannot be made using the Section 505(j) approval criteria, but are routinely made under Section 505(b).

As Dr. Cone explains in his Declaration:

> If a proposed product utilizes conceptually different approaches to deterrence from those of reformulated OxyContin, then the proposed product will likely fail some or all of the tests that measure the deterrent properties of OxyContin. Similarly, there is no point in subjecting OxyContin to tests designed to measure, for instance, the release from a proposed product of added ingredients intended to cause physical irritation or harm to abusers. In such an "apples and oranges" situation, the only way to evaluate relative effectiveness in deterring abuse would be through

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[82] Response to Petitions, Docket Nos. FDA-2007-P-0128; FDA-2009-P-0040 (July 29, 2009), at pp. 6, 7, 9, 10, 11. *See also* Draft Guidance on Fluticasone Propionate: Salmeterol Xinafoate, September 2013 at pages 5-6, available at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm367643.pdf (functional equivalence of drug administration system features required as a prerequisite to 505(j) eligibility).

epidemiologic outcomes data which, of course, could only be generated after the alternate product was in widespread distribution. Therefore, it is my opinion that such conceptually different alternate products should be considered entirely on their own merits, *i.e.*, in an NDA context, and not as potential equivalents. On the other hand, proposed products which use different technological approaches to achieve the physicochemical attributes which deter abuse of reformulated OxyContin can be readily compared through the test methods described here and, if shown to be no worse than reformulated OxyContin in those tests, can reasonably be considered equivalent on that basis.[83]

Conclusion

The original formulation of OxyContin was the subject of abuse, misuse, and diversion. Purdue took a number of steps to address these serious problems. One of the most difficult and ambitious efforts was a targeted research and development program to create a new type of formulation that was bioequivalent to the original when taken as directed by patients, but was resistant to common forms of tampering that precede many forms of abuse and misuse. The resulting product, reformulated OxyContin, is very difficult to break or crush, retains controlled-release properties when it is physically manipulated or reduced to small particles, resists dissolution, and instead forms a viscous hydrogel in the presence of liquid that impedes use by nasal or intravenous routes of administration.

With the submission of ANDAs citing reformulated OxyContin as the RLD, the Agency must decide how proposed generic versions of the product should be evaluated under the applicable statutory standards, in order to preserve the important safety advantages represented by reformulated OxyContin. This Petition requests that the abuse-deterrent attributes of proposed generic copies be comprehensively evaluated through specified comparative *in vitro* and *in vivo* testing, and documented, in each test, to perform as least as well as OxyContin under conditions designed to simulate tampering.

FDA has already made clear, as a matter of law and of public health policy, that a proposed generic version of reformulated OxyContin, which does not have demonstrated abuse-deterrent features at least as robust and comprehensive as OxyContin, cannot properly be approved. This Petition requests relief that similarly prevents such approvals.

At the same time, the requested relief would not restrict the ability of generic applicants to employ alternate technological means of achieving the same functional results. Consistent with Dr. Throckmorton's remarks during a June 2013 Congressional

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[83] Appendix A, ¶ 9, n 4.

hearing and remarks at the AD Science Meeting, this Petition advocates an approach that turns on the demonstrated functional properties of proposed generic products, rather than equivalency of technology. However, proposed generic products that have not been shown, through the studies discussed in this Petition, to perform as well as OxyContin under conditions designed to simulate tampering do not have the same risk-benefit profile as OxyContin, are not as safe as OxyContin, and do not have the same performance characteristics as OxyContin. Such products cannot duplicate the "Abuse Deterrence Studies" section of OxyContin labeling, as required by the Hatch-Waxman Amendments and FDA's implementing regulations. Neither can those products be considered the "same dosage form" as OxyContin, "bioequivalent" to OxyContin, or to have inactive ingredients or formulations as safe as OxyContin. In short, such products are not generic copies of reformulated OxyContin and may not be approved as such.

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.

Economic Impact

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

Certification

I certify that, to my best knowledge and belief: (a) this petition includes all information and views upon which the petition relies; (b) this petition includes representative data and/or information known to the petitioner which are unfavorable to the petition; and (c) I have taken reasonable steps to ensure that any representative data and/or information that are unfavorable to the petition were disclosed to me. I further certify that the information upon which I have based the action requested herein first became known to the party on whose behalf this petition is submitted on or about the following date:

September 21, 2006: First receipt, internal to Purdue, of initial *in vitro* data characterizing the physicochemical properties of reformulated OxyContin.

May 3, 2008: First public presentation of initial *in vitro* data characterizing the physicochemical properties of reformulated OxyContin.

May 5, 2008: Advice from Advisory Committee concerning the *in vitro* experiments that should be conducted to adequately characterize the physicochemical properties of reformulated OxyContin.

October 3, 2008: CRL from FDA stating requirements for *in vitro* experiments to adequately characterize the physicochemical properties of reformulated OxyContin.

December 31, 2008: First receipt, internal to Purdue, of data from second set of *in vitro* experiments characterizing the physicochemical properties of reformulated OxyContin.

September 22, 2009: First public presentation of data from second set of *in vitro* experiments characterizing the physicochemical properties of reformulated OxyContin.

March 1, 2010: First receipt, internal to Purdue, of *in vivo* data from pharmacokinetic and abuse potential study of reformulated OxyContin.

July 15, 2010: FDA publication of a draft bioequivalence guidance for oxycodone hydrochloride extended-release tablets.

February 8, 2011: First notice of Paragraph IV certifications included in ANDAs citing reformulated OxyContin as the Reference Listed Drug, including information about proposed generic products.

April 27, 2011: First receipt, internal to Purdue, of preliminary epidemiologic data from studies of the impact of reformulated OxyContin.

June 1, 2011: First conference with Dr. Edward Cone concerning the type of data that ought to be required to support approval of a generic version of reformulated OxyContin.

September 7, 2011: First public presentation/publication of preliminary epidemiologic data from studies of the impact of reformulated OxyContin.

May 10, 2012: First publication (web posting) of *in vivo* data from pharmacokinetic and abuse potential studies of reformulated OxyContin.

June 13, 2012: Presentation of updated results from several epidemiologic studies of the impact of reformulated OxyContin.

June 14, 2012: FDA publication of bioequivalency guidance for Embeda (morphine sulfate; naltrexone hydrochloride).

January 9, 2013: FDA publication of *Guidance for Industry: Abuse-Deterrent Opioids – Evaluation and Labeling,* Draft Guidance

January 23, 2013: Non-substantive denial of Petition docketed as Docket No. FDA-2012-P-0939

February 22, 2013: Petition for Reconsideration, Docket No. FDA-2012-P-0939

April 16, 2013: Approval of changes to the label of reformulated OxyContin.

April 16, 2013: FDA publication of its determination that the original formulation of OxyContin was withdrawn from sale for reasons of safety or effectiveness.

April 16, 2013: Memorandum of Douglas C. Throckmorton re: Abuse-Deterrent Properties of Purdue's Reformulated OxyContin (oxycodone hydrochloride) Extended-Release Tablets

April 22, 2103: Publication of article in The Pink Sheet, *Generic OxyContin Criteria Being Developed By FDA Working Group*

May 10, 2013: FDA publication of its determination that the original formulation of Opana ER was not withdrawn from sale for reasons of safety or effectiveness

June 14, 2013: Testimony of Douglas Throckmorton before the Health Subcommittee of the House Energy and Commerce Committee

August 5, 2013: First conference with Dr. Edward Cone concerning updated recommendations as to the type of data that ought to be required to support approval of a generic version of reformulated OxyContin.

September 9, 2013: FDA publication of draft bioequivalence guidance on Fluticasone Propionate: Salmeterol Xinafoate.

September 30, 2013: Remarks and Presentations at the Abuse Deterrent Formulation Science Meeting.

October 1, 2013: Remarks and Presentations at the Abuse Deterrent Formulation Science Meeting.

If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: Purdue Pharma L.P.

I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

Peter R. Mathers
Counsel to Purdue Pharma L.P.

Respectfully submitted,

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Counsel to Purdue Pharma L.P.

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Exhibits

Exhibit 1	Coplan, P.M., *Design of a Post-Marketing Study Program to Assess the Effects of a Reformulated Extended-Release Oxycodone Tablet on its Abuse,* presented at 28th International Conference on Pharmacoepidemiology & Therapeutic Risk Management, August 23-26, 2012, Pharmacoepidemiology and Drug Safety 2012; Vol. 21 (Supp. 3), p. 446, Abstract # 963 and Poster

Appendices

Appendix A	Declaration of Edward J. Cone, Ph.D, with Exhibits A-1 to A-4
Appendix B	Pharmacokinetic and Abuse Potential Studies of Reformulated OxyContin, with Exhibits B-1 through B-4
Appendix C	Epidemiologic and Other Studies of the Real World Impact of Reformulated OxyContin, with Exhibits C-1 through C-15

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