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July 13, 2012

Via Overnight Mail

Dockets Management Branch
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, 314.94, 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. Purdue is also the holder of New Drug Application # 20-553 for the original formulation of OxyContin, which is now discontinued.

The original, now discontinued, formulation of OxyContin was safe and effective when taken as directed.[1] However, the original formulation of OxyContin was subject to

[1] Though the original formulation was safe, that formulation has been withdrawn from sale for safety reasons and therefore NDA # 20-553 covering the original formulation may no longer be referenced in support of an ANDA. *See* Comments of Purdue Pharma L.P. on pending petitions docketed as FDA-2010-P-0526, FDA-2010-P-0540, and FDA-2011-P-0473, available at: http://www.regulations.gov/#!docketDetail;D=FDA-2010-P-0526;dct=FR%252BPR%252BN%252BO%252BSR and http://www.regulations.gov/#!docketDetail;D=FDA-2010-P-0540;dct=FR%252BPR%252BN%252BO%252BSR and http://www.regulations.gov/#!searchResults;rpp=25;po=0;s=fda-2011-p-0473. As explained in those cited docket submissions, in the context of a replacement product, a determination that a product was withdrawn from sale for safety reasons under 21 U.S.C. § 355(j)(7)(C) and 21 C.F.R. § 314.161 requires only a finding that the replacement product is intended to have a more favorable risk/benefit analysis than the original, and that the original was withdrawn from sale for that reason. In the case of OxyContin, it cannot reasonably be disputed that the reformulation was intended to have a more favorable risk/benefit profile than the original formulation. Moreover, as detailed in this Citizen Petition, epidemiologic and other data now confirm that reformulated OxyContin in fact has a more favorable risk/benefit profile than the original formulation.

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significant abuse and diversion. In addition to intentional abuse, there were instances in which the original formulation of OxyContin was inadvertently misused by legitimate patients or their caregivers. Purdue took a number of steps intended to mitigate these risks, including development of a reformulation designed to resist common methods of tampering by someone trying to intentionally abuse the product, or by a patient/caregiver inadvertently misusing the medication. Reformulated OxyContin has been extensively tested under a variety of *in vitro* conditions designed to simulate attempts to abuse or misuse the product, and was also tested in pharmacokinetic and abuse potential studies. Based on these data, Purdue believes that the reformulated product offers substantial safety advantages over the original. Data from an extensive and ongoing epidemiological monitoring program are already confirming that reformulated OxyContin is subject to less misuse and abuse than original OxyContin.

Several abbreviated new drug applications that cite reformulated OxyContin, NDA # 22-272 as the Reference Listed Drug have been submitted to FDA.[2] Purdue submits this Citizen Petition to ensure that, prior to approval, all purported generic copies of reformulated OxyContin are also subject to a rigorous *in vitro* test program and an appropriate confirmatory *in vivo* study or studies, and that the results of such testing indicate that the generic products can be expected to perform as well as reformulated OxyContin when subjected to manipulations by individuals intent on abusing the product or by patient/caregivers inadvertently misusing the medication.

[2] Purdue learned of these filings directly from sponsors who have provided Purdue with notification of their filing of ANDAs containing patent certifications under 21 U.S.C. § 355(j)(2)(A)(vii)(IV).

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I. Action Requested

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

(1) Adopt and announce a guidance detailing *in vitro* and *in vivo* tests that must be performed to characterize the physicochemical properties of the proposed generic product and to assess the release of oxycodone when the product is manipulated in order to simulate attempts to tamper with the product for purposes of abuse or misuse.[3]

(a) The guidance should require performance of *in vitro* tests that are consistent both with the requirements imposed upon Purdue in the Agency's October 3, 2008 Complete Response Letter and with the *in vitro* tests performed by Purdue on OxyContin. The *in vitro* tests required should be comparative, using the reference listed drug OxyContin (NDA # 22-272) as a control.

(b) The guidance should require initial testing comparing the bioavailability of finely crushed generic product finely crushed reformulated OxyContin (NDA # 22-272) following oral administration. Results of this initial *in vivo* test as well as the results of the *in vitro* experiments discussed in (a) above, and the specific physical and chemical attributes of the proposed generic product, should then be considered to determine whether additional *in vivo* testing of different tampered states (*e.g.*, coarsely crushed) and/or different routes of administration (*e.g.*, intranasal) are necessary to adequately assess whether the proposed generic product can be expected to perform as well as reformulated OxyContin when subjected to known and anticipated forms of tampering.

(c) The guidance should require that generic products pass statistical analyses which demonstrate that they exhibit no greater rate or extent of oxycodone release than OxyContin (NDA #22-272) in the specified *in vitro* and *in vivo* tests.

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[3] 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 ANDA applicants.

(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 required by the guidance (or, in the absence of published guidance, conduct the tests and meet the statistical acceptance criteria described in section (1) above), or (b) includes data from such tests which fail to meet those acceptance criteria.

(3) If the Agency approves an application for any drug product which might otherwise be considered pharmaceutically equivalent to reformulated OxyContin (NDA # 22-272) but which application either does not include data from *in vitro* and *in vivo* tests described in (1) above, or includes data from such tests which fail to demonstrate that the product performs as least as well as reformulated OxyContin following product manipulation, assign a BX code, indicating that the product is not therapeutically equivalent to OxyContin.[4]

(4) To the extent that the Agency determines that the required *in vitro* and/or *in vivo* tests are considered bioequivalence requirements, modify the draft bioequivalence guidance on oxycodone extended release tablets[5] to reflect those test requirements.

II. Statement of Grounds

A. Factual Background

1. OxyContin (oxycodone HCl controlled-release) Tablets – Purdue's Original Extended-Release Oral Formulation of Oxycodone

The original formulation of OxyContin was approved in December 1995 for the management of moderate to severe pain where use of an opioid analgesic is appropriate for more than a few days. Subsequently, the indication was modified to: "the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time." OxyContin was the first extended-release oxycodone product approved for marketing in the United States.

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[4] Purdue believes that the risks of such products outweigh any potential benefits, and urges the Agency to refuse to approve such an application. Should the Agency nevertheless consider approving such an application, it will have to address several issues, *e.g.*, the need for additional *in vivo* studies to characterize the performance, abuse potential and/or desirability of the product following manipulation, the need for post-marketing epidemiologic studies, and the need for the application to be filed and considered, if at all, under Section 505(b)(2) of the Act. This Petition does not address these important considerations.

[5] *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.

Purdue's NDA for the original version of OxyContin (NDA # 20-553) provided for 10, 20 and 40 mg tablets. In 1996 and 2000, FDA approved two supplements providing for 80 and 160 mg tablets, respectively. Thereafter, in September 2006, FDA approved a supplement providing for three intermediate strength tablets: 15, 30, and 60 mg.

Unlike immediate release oxycodone formulations that must be dosed every 4-6 hours, OxyContin provides a controlled release of oxycodone that allows for dosing every twelve hours. Control of the release of oxycodone from the original OxyContin was achieved by formulating the active ingredient in a polymeric matrix that allows release in the gut over time. The original tablet must be taken intact for the release of oxycodone to be controlled as intended.

2. Abuse and Misuse of the Original Formulation of OxyContin

Along with other strong opioids, such as fentanyl-, morphine-, and hydromorphone-based products, the original formulation of OxyContin was subject to Schedule II (CII) controls under the Controlled Substances Act, 21 U.S.C. §§ 801, *et seq.* CII is the most restrictive classification available for approved products and raises the overall level of security and other controls applicable to all parties involved in the manufacturing, distribution, prescription, and dispensing of the product. As a CII drug, OxyContin, like other products in its class, has "a high potential for abuse" and such abuse "may lead to severe psychological or physical dependence." 21 U.S.C. § 812.

In January 2001, approximately five years after the launch of OxyContin, the Drug Enforcement Administration published an *Information Bulletin* describing abuse and diversion of OxyContin as a significant problem.[6] In addition to intentional abuse, there were instances in which the original formulation of OxyContin was inadvertently misused by legitimate patients or their caregivers. In 2008, FDA's Division of Medication Error Prevention analyzed data from the Agency's Adverse Event Reporting System ("AERS") database. The analysis revealed that more than 10% of reported cases of manipulation of OxyContin involved healthcare professionals manipulating OxyContin for ease of patient administration (*e.g.*, crushing for administration through a gastric tube).[7] Similarly, Purdue's internal database of adverse events reported in post-

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[6] *See Information Bulletin, OxyContin Diversion and Abuse,* 2001-L0424-001 (Jan. 2001), available at: http://www.justice.gov/ndic/pubs/651/index.htm#Contents.

[7] Memorandum to B. Rappaport, Director, Division of Analgesics, Anesthetics, and Rheumatology Products from K. Arnwine, Acting Team Leader and L. Kim-Jung, Team Leader, Division of Medication Error Prevention (April 7, 2008) at 4, available within: http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4356b1-01-FDA.pdf.

marketing experience includes numerous cases of tablet manipulation by or for legitimate patients, such as crushing for administration in soft foods or via a gastric tube.[8]

Understanding and addressing the problems of abuse, misuse, and diversion of OxyContin has been a significant priority for Purdue. As reports 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, developing and implementing a comprehensive Risk Management Plan to further foster the safe prescribing and use of OxyContin. Since 2001, Purdue has continued to engage in risk management activities to address, *inter alia*, the risks associated with the abuse and misuse of extended release oxycodone. These initiatives support the education of healthcare professionals and consumers, the monitoring and tracking of prescription medication, the proper storage and disposal of prescription medications, and the appropriate and effective enforcement of existing laws and regulations governing the use of opioid analgesic medications. Additionally, OxyContin historically was subject to a product-specific Risk Evaluation and Mitigation Strategy ("REMS") and is now subject to the class REMS for long-acting and extended-release opioid drug products approved by the Agency on July 9, 2012.

3. Development and Regulatory Review of Purdue's New Formulation of Extended-Release Oxycodone

Purdue also began development work on a new formulation of OxyContin intended to discourage misuse and abuse. Crushing or chewing the original formulation could readily overcome the extended-release mechanism and release the oxycodone dose, effectively making it an immediate-release product.[9] Purdue evaluated several reformulation strategies intended to mitigate this vulnerability, and ultimately pursued approval for a formulation with a different inert excipient that changes the physicochemical properties of the tablets when subjected to a specific manufacturing process.

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[8] *See, e.g.*, Transcript of Joint Meeting of the Anesthetic and Life Support Drugs Advisory Committee (ALSDAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM) (Sept. 24, 2009), pp. 264-266, available at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndLifeSupportDrugsAdvisoryCommittee/UCM187082.pdf.

[9] 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 16, 2, available at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndLifeSupportDrugsAdvisoryCommittee/UCM230110.pdf.

The reformulated OxyContin, now approved under NDA # 22-272, contains a specific form of the polymer polyethylene oxide. During the manufacturing process, the tablet is heated above the melting point of the polymer. On cooling, the polymer fuses to impart plastic-like properties to the tablet. The tablets are difficult to break or crush and are only deformed by most manual methods such as striking with a hammer. Attempts at manipulation by crushing generally lead to deformed tablets, instead of fine powder. These deformed tablets retain some degree of controlled-release properties. Also, the formulation forms a viscous hydrogel when hydrated, which is a significant detriment to abuse by the intranasal route. Further, a viscous gel is formed even in small volumes of water, making it difficult or impossible to prepare for injection with needles commonly used by abusers. The reduced rate of release of oxycodone from the reformulated tablets (compared to the original OxyContin formulation), when manipulated, was designed and is expected to deter abuse.[10]

Due to its physicochemical properties, the reformulated product is more difficult to prepare for abuse via multiple routes of administration. Specifically, the reformulation "was designed primarily to frustrate those who chew or crush tablets prior to swallowing, those who crush tablets and inhale the resultant powder, and those who crush tablets, dissolve the powder and inject it."[11] In addition, the reformulated OxyContin tablets are less likely to be inadvertently crushed by patients or caregivers, and are therefore intended to provide safety benefits to patients. In particular, the reformulated tablets are intended to impede chewing or crushing tablets for patient administration and splitting tablets in order to make a prescription last longer or reduce the dose, as well as provide a longer window for recognition of a problem and emergency care in the case of inadvertent chewing. [12]

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[10] Purdue Pharma L.P., Meeting Background Material, May 5, 2008 joint meeting of the Anesthetic and Life Support Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee, at 15, available at: http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4356b1-02-Purdue.pdf and 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 16, available at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndLifeSupportDrugsAdvisoryCommittee/UCM230110.pdf.

[11] Purdue Pharma L.P., Meeting Background Material, May 5, 2008 joint meeting of the Anesthetic and Life Support Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee, at 14, available at: http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4356b1-02-Purdue.pdf.

[12] Purdue Pharma L.P., Meeting Background Material, May 5, 2008 joint meeting of the Anesthetic and Life Support Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee, at p. 29, available at: http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4356b1-02-Purdue.pdf.

An NDA for reformulated OxyContin was submitted to FDA in November 2007. The NDA included data showing that the new formulation is bioequivalent to the original formulation of OxyContin Tablets 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.

Purdue's initial *in vitro* test program was designed to simulate a wide range of physical and chemical methods that could be employed in an attempt to compromise the controlled-release mechanism of the tablets. The range of tests extended from those methods considered relatively simple to perform to those requiring advance planning, mechanical equipment, multiple steps for extraction of the active drug substance, and solvents not typically available to the general public. All strengths of reformulated OxyContin were tested, along with the original formulation of OxyContin. The tests included methods to crush or mill the tablets, simulated preparation for intravenous abuse, and multiple extraction studies. The extraction studies used equipment and solvents readily available to the general public and relatively short extraction times at room temperature, as well as more advanced extraction techniques using less available or more harmful solvents, longer extraction times, and elevated temperatures.[13] The Advisory Committee concluded that the available data were not adequate to evaluate whether reformulated Oxycontin is likely to reduce abuse, misuse, or diversion. Some Committee members indicated that more rigorous testing was needed, and some stated that the *in vitro* test methods employed should be independently validated.[14]

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[13] *Id.* at pp. 16-26.

[14] 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.

Following the Advisory Committee meeting, FDA issued a Complete Response letter requesting substantial additional data to characterize the physicochemical properties of the tablets. Specifically, FDA's October 2008 letter[15] stated the following requirements:

> Provide studies of the new formulation that demonstrate the effects of physical and/or chemical manipulation and that incorporate the following:
>
> a. The testing must be conducted in a blinded manner, preferably by an independent third party.
>
> b. The methods used to assess the physical characteristics of the product must be reassessed. Consult individuals experienced in the intentional extraction of oxycodone from OxyContin for abuse to determine the methods for testing that will most likely replicate the methods encountered once the product is marketed. The resultant testing methods should then undergo a validation procedure to ensure they are conducted in a reproducible and meaningful manner.
>
> c. Consult experts on extraction techniques to fully assess your proposed extraction testing protocols and to evaluate the data upon completion.
>
> d. Provide data documenting the amount of oxycodone released if the reformulated tablet is chewed . . . . .
>
> e. Conduct studies to determine the relative rate of release of the active pharmaceutical ingredient from all strengths of crushed . . . tablets to determine whether all dosage strengths retain the controlled-release properties after crushing . . . and that dose dumping does not occur. . . . .

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[15] The text of the Complete Response letter provided in this Petition is taken from the FDA's publicly posted review of NDA # 22-272. *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.
The version publicly released by FDA omits certain information about specific test methods. This Petition omits that same information, in an effort to avoid providing specific details that might be used by abusers to intentionally extract oxycodone from reformulated OxyContin. Omissions are identified with ellipses. As noted in footnote 3 above, should more detailed information concerning recommended test methodology be required, the Agency may reasonably conclude that such additional detail should be provided only in confidential communications with potential ANDA applicants.

f. Provide data documenting how altering the grinding conditions, . . . might affect the final particle size distribution of the tablets for all strengths and whether these efforts might render a product suitable for insufflation.

Purdue took immediate steps to conduct the additional testing recommended in the above-referenced section of the Complete Response letter, and agreed to complete the studies expeditiously. However, Purdue also requested that FDA not require completion of the studies prior to approval of reformulated OxyContin, because that would delay the introductory launch of the reformulation, and in light of Purdue's intention to exclude from initial product labeling all information regarding the tamper-resistant physicochemical properties of the tablets. This request was not granted. Instead, Purdue was required to comply with the additional test requirements before reformulated OxyContin would be approved.[16]

Purdue discussed the additional *in vitro* test requirements further with FDA in a January 21, 2009 meeting.[17] Purdue also 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.[18] One of the primary advisors to Purdue in this regard was Dr. Edward J. Cone, whose Report and Declaration are attached hereto as Exhibit 22.

Based on input from independent experts and the May 2008 Advisory Committee, and in accordance with the requirements of the Complete Response letter, Purdue conducted its additional extensive battery of *in vitro* experiments to characterize the

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[16] Indeed, FDA convened a second joint meeting of the Anesthetic and Life Support Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee to evaluate the new *in vitro* data generated in accordance with the requirements stated in the Complete Response letter and vote on whether FDA should approve the product, despite Purdue's proposed labeling omitting any mention of the tamper-resistant physicochemical attributes of reformulated OxyContin. *See* Memorandum to Advisory Committee members from Bob A. Rappaport, M.D. (Aug. 25, 2009), at pp. 1-2, available at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM183204.pdf.

[17] Purdue Pharma L.P., FDA Advisory Committee Briefing Document on NDA 22-272 (reformulated OxyContin® tablets) (Sept. 24, 2009) at 21-22, available at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndLifeSupportDrugsAdvisoryCommittee/UCM183205.pdf.

[18] *Id.* at pp. 22-23.

physicochemical properties of reformulated OxyContin. After internal validation of the protocols to ensure reproducibility and consistency across experiments, methods were standardized and transferred to outside laboratories. The vast majority of the tests were performed by these independent outside laboratories, and personnel performing the experiments were blinded to the fullest extent possible. The protocols encompassed seven groups of studies that 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. In particular, these seven groups of studies are:[19]

(1) Fractionation of Tablets – This series of tests used a variety of household instruments to attempt to reduce the particle size of reformulated OxyContin. The effect of temperature on ability to reduce particle size was also evaluated. Resulting particles were sieved to segregate discrete bands of similar-sized particles. These distinct bands represent the full range of particle sizes likely achievable during preparation for misuse, accidental or otherwise, by the general population. To ensure that subsequent experiments were standardized and reproducible, standardized methods were developed to reproduce these discrete bands for use in the other groups of studies.

(2) Extraction – This series of tests evaluated the oxycodone release characteristics of reformulated OxyContin following extraction in a variety of readily available solvents. The experiments were performed for all dosage strengths covering the range of particle size bands at room temperature and at elevated temperature. Extraction was performed in standardized volumes of liquid, and multiple time points were sampled to generate a kinetic representation of API release. The endpoints for these experiments were defined as the time to complete release of API from the sample.

(3) Dissolution in Ethanol – These experiments were designed to characterize the release of oxycodone in various solutions containing ethanol. All bands from all strengths of reformulated OxyContin were tested and multiple time points were sampled to generate a kinetic representation of API release. Sampling was continued until no further API release was observed.

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[19] Additional detail about the seven groups of studies conducted by Purdue 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. *See* footnote 3 above.

(4) Extraction in Advanced Solvents – This series of tests evaluated extraction in a variety of solvents that are not directly ingestible. The experiments were performed for all dosage strengths of various particle size bands at room temperature and at elevated temperature. Extraction was performed in standardized volumes of liquid, and multiple time points were sampled to generate a kinetic representation of API release.

(5) Syringability, Injectability, and Extraction after Vaporization – These experiments were designed to simulate preparation for intentional intravenous and inhalation abuse. The goals of these experiments were to determine both how much API could be loaded and delivered via syringe for intravenous abuse at room temperature and elevated temperature and how much API is released after vaporization of reformulated OxyContin. All dosage strengths of the smallest particle size band were studied in these experiments. Syringability was assessed by attempting to aspirate various mixtures with various gauge needles. Injectability was assessed by preloading syringes with various mixtures and expelling the material through various gauge needles. Inhalation was simulated using a laboratory apparatus. Oxycodone content of resulting vapors and residual material was assessed.

(6) Complex Extraction of Oxycodone using Advanced Techniques – This series of tests was designed to determine the maximum amount of oxycodone that could be recovered through use of advanced techniques. All dosage strengths of the smallest particle size band were studied in these experiments.

(7) Complex Extraction with Advanced Solvents Using Liquid Phase Extraction – These experiments were conducted on all dosage strengths of the smallest particle size band to determine the maximum amount of oxycodone that could be recovered using a liquid phase extraction technique.

The *in vitro* data from these seven groups of studies indicate 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.[20]

Purdue submitted the additional *in vitro* data specified in the Complete Response letter on March 30, 2009. FDA convened a second joint meeting of Anesthetic and Life Support Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee to review the *in vitro* data characterizing the physicochemical properties of the new formulation and vote on whether FDA should approve the product.

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[20] 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.

A memorandum authored by the Director, Division of Anesthesia, Analgesia and Rheumatology Products, Center for Drug Evaluation and Research (the Division responsible for review of NDA ##20-553 and 22-272) describes the conclusions of the Committees as follows:

> The consensus of the committee was that the reformulated product (all strengths) demonstrated an incremental increase in tamper-resistance, although it clearly maintained the previously acknowledged high risk for people who misused or abused the product by taking higher than safe doses of intact tablets. The advantages of the new formulation include:
>
> - Perhaps most importantly, it cannot be crushed or chewed by standard mechanisms that may result in the ingestion of a lethal "immediate-release" dose by a casual or recreational abuser, or by a patient, e.g., when a nurse or caretaker attempts to crush and administer via a nasogastric tube.
> - It cannot be altered to a consistency (i.e., powder) that can be insufflated or dissolved for injection using the standard household tools that the more hard-core abusers generally use.
> - When dissolved in water it becomes a thick, gelatinous substance that cannot be syringed or injected with the usual needles and syringes used by hard-core abusers.
>
> The committee members acknowledged that the reformulated OxyContin tablets can be crushed and/or extracted by unusual means and, therefore, those intent on abusing the products by defeating the extended-release mechanism will still be able to do so. The committee members also acknowledged that those abusing or misusing the product by ingesting more intact tablets or higher doses of intact tablets would not be provided with any protection from overdose with this reformulated product. Finally, the committee members were generally in consensus that a post-marketing epidemiology study to assess the impact of the reformulation on actual abuse in the community is essential to fully understand the value of the product and the level of risk management it will need, and that this study should be required as post-marketing requirement for approval.[21]

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[21] 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.

4. FDA Approval and Purdue's Launch of the New Formulation of Extended-Release Oxycodone

Following review at the September 24, 2009 Advisory Committee Meeting, the new formulation was approved in April 2010. NDA # 22-272 provides for 10, 15, 20, 30, 40, 60, and 80 mg tablets. Reformulated OxyContin, like the original, is indicated for management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time, and is not for use on an as-needed basis or in the immediate post-operative period.

Upon approval in April 2010, FDA issued a press release stating:

> The U.S. Food and Drug Administration today approved a new formulation of the controlled-release drug OxyContin that has been designed to help discourage misuse and abuse of the medication.
>
> OxyContin is made to slowly release the potent opioid oxycodone to treat patients who require a continuous, around-the-clock opioid analgesic for management of their moderate to severe pain for an extended period of time. Because of its controlled-release properties, each OxyContin tablet contains a large quantity of oxycodone, which allows patients to take their drug less often. However, people intent on abusing the previous formulation have been able to release high levels of oxycodone all at once, which can result in a fatal overdose and contributes to high rates of OxyContin abuse.
>
> The reformulated OxyContin is intended to prevent the opioid medication from being cut, broken, chewed, crushed or dissolved to release more medication. The new formulation may be an improvement that may result in less risk of overdose due to tampering, and will likely result in less abuse by snorting or injection; but it still can be abused or misused by simply ingesting larger doses than are recommended.
>
> "Although this new formulation of OxyContin may provide only an incremental advantage over the current version of the drug, it is still a step in the right direction," said Bob Rappaport, M.D., director of the Division of Anesthesia and Analgesia Products in the FDA's Center for Drug Evaluation and Research.
>
> "As with all opioids, safety is an important consideration," he said. "Prescribers and patients need to know that its tamper-resistant properties

are limited and need to carefully weigh the benefits and risks of using this medication to treat pain."

According to the U.S. Substance Abuse and Mental Health Services Administration's National Survey on Drug Use and Health, approximately half a million people used OxyContin non-medically for the first time in 2008.

The manufacturer of OxyContin, Purdue Pharma L.P., will be required to conduct a postmarket study to collect data on the extent to which the new formulation reduces abuse and misuse of this opioid. The FDA is also requiring a REMS (Risk Evaluation and Mitigation Strategy) that will include the issuance of a Medication Guide to patients and a requirement for prescriber education regarding the appropriate use of opioid analgesics in the treatment of pain.

Purdue Pharma is based in Stamford, Conn.[22]

Two months later, FDA featured reformulated OxyContin in its video publication Patient Safety News. The video states:

FDA has approved a new formulation of the controlled-release drug OxyContin that is designed to be more difficult to manipulate by someone trying to misuse or abuse the medication. OxyContin tablets contain the opioid analgesic oxycodone, which is released gradually after the tablet is swallowed. People intent on abusing the drug have been able to release more of the medication all at once by crushing or chewing the tablets, or by dissolving them and injecting the liquid.

The new formulation makes it more difficult for people to defeat the controlled-release properties of the drug by cutting or crushing the tablets. And if someone tries to dissolve the tablets, the result will be a gummy substance that would be difficult to inject through a syringe. Although the new formulation may not prevent all abuse of OxyContin, it is a step in the right direction. The manufacturer will conduct a study to evaluate how well the new formulation reduces abuse and misuse of the drug.[23]

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[22] *FDA Approves New Formulation for OxyContin* (April 5, 2010), available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm207480.htm.

[23] 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.

Purdue began shipment of reformulated OxyContin in August 2010, with the objective of minimizing the time for overlap of the two formulations at the retail level while ensuring that patient access to their medicine was uninterrupted.[24] During the week ending December 24, 2010, 92.3% of total OxyContin prescriptions dispensed were filled with the new formulation, increasing to over 99% by October 2011. Purdue has not distributed the original formulation of OxyContin in the United States since early August 2010 and that formulation now appears in the "Discontinued" section of the Orange Book.[25]

5. Epidemiologic Studies of the Impact of Reformulated OxyContin

Purdue is conducting eleven epidemiologic studies, six of which are required by post-marketing commitments to the Agency. These eleven studies are designed to assess the effects of the new formulation on misuse and abuse of OxyContin and their potential consequences of addiction, overdose, and death. The studies were designed with the assistance of external experts and are intended to generate a comprehensive picture of the effects of the reformulation on abuse.[26] Thus far, data from six epidemiologic studies have been made available publicly in abstracts and posters submitted to professional associations. Information on these six studies is provided below. After additional data from these six studies, or the other ongoing epidemiologic studies are published, we plan to file the reports as supplements to this Petition.

Collectively, these data from ongoing studies 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, following the introduction of reformulated OxyContin, the epidemiologic study data show:

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[24] 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 15, available at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndLifeSupportDrugsAdvisoryCommittee/UCM230110.pdf.

[25] While Purdue no longer sells the original formulation in the United States, its associated companies do sell the original formulation in countries where the new formulation is not approved.

[26] *See* 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.

- 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 adverse events involving OxyContin.
- Reduction in unintentional poisonings and adverse events involving OxyContin, including therapeutic errors.

These 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.

These six studies are described below and in the attached published abstracts[27] and posters. For the convenience of the reader, Section (f) below includes a summary of the study results in table format.

(a) Exposures Reported to Poison Centers

Regional Poison Centers are staffed twenty-four hours a day, seven days a week with trained healthcare professionals who field calls from consumers and healthcare practitioners. These Poison Centers gather data collected during the course of providing callers with specific exposure management recommendations.[28] Each poison center utilizes a nationally standardized data collection tool through which the reason for each exposure is coded. Exposures coded as intentional are further classified as suspected suicide, misuse, abuse, or unknown. Exposures coded as unintentional are further classified as therapeutic error, misuse, general, or unknown.[29] Calls to Poison Centers reporting that an individual was exposed to a product and seeking emergency advice or

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[27] Certain of the attached abstracts refer to OxyContin as "ER oxycodone" in accordance with the conferences' preference for use of generic names rather than brand names. OxyContin will be used in this Petition for clarity. However, a small amount of previously-marketed non-tamper resistant generic versions of the original OxyContin formulation may have been included within these data.

[28] Background information on the methodology used to collect data on exposures reported to poison centers is available in Bronstein, Alvin C. *et al., 2010 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 28th Annual Report,* Clin. Tox. (2011), 49, 910-941, at pp. 914-916, available at: http://www.aapcc.org/dnn/Portals/0/2010%20NPDS%20Annual%20Report.pdf.

[29] The standardized data collection tool includes additional categories, most of which are inapplicable to drug exposures (*e.g.*, "unintentional – bite/sting" and "unintentional – food poisoning"). *See id.* at p. 924, Table 6A.

help, and documented in this way, are a proxy measure for adverse events associated with medical or nonmedical use of a product or drug class.

Two organizations compile data collected by Poison Centers. The Researched Abuse Diversion and Addiction-Related Surveillance (RADARS®) System collects Poison Center data reflecting exposures to prescription drugs. The RADARS System is an independent, nonprofit operation of the Rocky Mountain Poison and Drug Center, a division of Denver Health and Hospital Authority.[30] RADARS® obtains data on a quarterly basis from Poison Centers in the majority of states, covering approximately 86% of the U.S. population.[31] The American Association of Poison Control Centers compiles data from all Poison Centers in the United States into a database known as the National Poison Data System ("NPDS"). The NPDS includes data on exposures to all types of substances, including cosmetics, cleaning supplies, pesticides, alcohol, plants, and prescription, over-the-counter, and illicit drugs.[32]

As discussed in detail in the sections that follow, data compiled by both organizations have been used to compare exposures to OxyContin before and after introduction of reformulated OxyContin. However, the published Poison Center data do not differentiate between exposures to original versus reformulated OxyContin in the period after the August 2010 launch of reformulated OxyContin, which impacts the reported data in two ways. First, both RADARS® and NPDS provide information on exposure rates adjusted for availability of product through legitimate channels. RADARS® adjusts for changes in drug availability by calculating rates per 1,000 unique recipients of dispensed drug ("URDD"), while NPDS provides rates adjusted by the number of prescriptions dispensed. It is important to appreciate that, in the case of reformulated OxyContin, these adjusted rates do not take into account the continued widespread availability of original OxyContin, through illicit channels, for an extended period following launch of reformulated OxyContin. In particular, the number of

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30 RADARS® was initially developed by Purdue as part of the company's response to increasing reports of abuse, misuse, and diversion of the original formulation of OxyContin. In 2006, the RADARS System was acquired by Denver Health and Hospital Authority and became an independent, nonprofit operation of the Rocky Mountain Poison and Drug Center.

31 Background on the RADARS® System Poison Center program is available on the RADARS® website at: http://www.radars.org/Home2/Programs/PoisonCenterProgram.aspx and also in Bailey, J. E., *The Underrecognized Toll of Prescription Opioid Abuse on Young Children,* Annals of Emergency Medicine, 2009;53:419-424, available at: http://www.cste.org/dnn/Portals/0/NTForums_Attach/Bailey%20et%20al%20Ann%20Emerg%20Med%202008%20In%20Press.pdf.

32 *See* Bronstein, Alvin C. *et al., 2010 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 28th Annual Report,* Clin. Tox. (2011), 49, 910-941, at p. 934, Table 17A, available at: http://www.aapcc.org/dnn/Portals/0/2010%20NPDS%20Annual%20Report.pdf.

exposures in the period after introduction of reformulated OxyContin continues to include exposures to original OxyContin, but the adjustments reflect a much quicker shift of dispensed prescriptions to reformulated OxyContin, among a decreasing total number of prescriptions. Second, the posters and abstracts published to date and discussed below compare average or mean exposures in the periods before and after introduction of reformulated OxyContin. Because the after-period averages or means include months in which original OxyContin continued to be widely available, comparisons using these averages or means underestimate changes over time during the period after introduction of reformulated OxyContin.

(1) Exposures Reported to Poison Centers in the RADARS® System

This study examined the RADARS® System Poison Center Program data to assess whether there was a change in the rate of abuse of OxyContin following launch of reformulated OxyContin.[33] Using these data, rates were calculated for intentional exposures coded as abuse and for other non-abuse intentional exposures. To adjust for changes in the RADARS® program coverage from quarter to quarter, rates per 100,000 population were calculated. To adjust for changes in drug availability, rates per 1,000 unique recipients of dispensed drug ("URDD") were calculated.

October 1, 2008 through September 30, 2010 was considered the period before introduction of reformulated OxyContin. In the data published to date, October 1, 2010 to December 30, 2011 was considered the period after introduction of the new formulation.

Based on these data, there was an estimated 34% decline in the average abuse rate per 100,000 population and an estimated 29% decline in the average abuse rate per 1,000 URDD after the introduction of reformulated OxyContin. These declines were greater than the changes observed for opioids other than OxyContin.

An analysis of data through the third quarter of 2011 also includes data on rates for other intentional exposures (non-abuse).[34] These data show an estimated 8% decline

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[33] Severtson, S. G., *et al., Reduced Abuse and Diversion Following the Reformulation of OxyContin®*, RADARS® System 6th Annual Meeting (April 24, 2012), available at: http://www.radars.org/Portals/1/OxyContin_ADF_Poster_20120424_FINAL.pdf and attached as Exhibit 5.

[34] Severtson, S. G., *et al. Decline in Rates of Abuse of Extended Release (ER) Oxycodone Following the Introduction of a Reformulated ER Oxycodone Product Using Data from the RADARS® System Poison Center Program,* International Association for the Study of Pain, 14th World Congress on Pain (August 27-31, 2012), [PF 088], available through http://www.abstracts2view.com/iasp/ and attached as Exhibit 4.

in the rate for OxyContin per 100,000 population and an estimated 3% decline in the average rate per 1,000 URDD.

(2) Exposures Reported to Poison Centers in the National Poison Data System

To assess whether there have been changes in the number of reported exposures associated with OxyContin, other single-entity (SE) oxycodone formulations (excluding OxyContin), and heroin following introduction of reformulated OxyContin, the NPDS data were used to evaluate the number of exposures reported to poison centers within the United States for these product categories before and after the August 2010 launch of reformulated OxyContin. Specifically, the one-year period from July 2009 through June 2010 was considered the pre-period, and the period from October 2010 onward is the post-period. Reports published to date include post-period data through December 2011, sixteen months after the launch of reformulated OxyContin.[35]

In the data reported through December 2011, all OxyContin exposures declined 22% in the post-period compared to the pre-period (from 693 to 540 cases per quarter). Similarly, intentional exposures declined 19% (from 391 to 316 cases per quarter) and intentional abuse exposures (a subset of intentional exposures) declined 30% (from 130 to 91 cases per quarter). Unintentional exposures declined 23% in the post-period compared to the pre-period (from 243 to 186 per quarter), therapeutic errors among patients (a subset of unintentional exposures) declined by 17% (161 to 134 per quarter), and unintentional general exposures (a subset of unintentional exposures and a marker of accidental exposures that result in calls to Poison Centers, mostly among children) declined by 38% (75 to 46 per quarter).

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[35] Coplan, P. *et al., National Changes in OxyContin, other Oxycodone, and Heroin Exposures Reported to Poison Centers with Introduction of Reformulated OxyContin®*, 74th Annual Scientific Meeting of the College on Problems of Drug Dependence, Abstract 121, available through: http://www.cpdd.vcu.edu/Pages/Meetings/CPDD12AbstractBook.pdf and Poster # 71 (presented June 13, 2012), attached collectively as Exhibit 1 (most current data provided in Poster).

Two other abstracts also report data from this study. Minor descrepancies between the references are attributable to rounding errors and a typographical error. *See* Coplan, P. *et al., Changes after Reformulation of Extended-Release Oxycodone in Calls to US Poison Centers for Oxycodone and Heroin,* International Association for the Study of Pain, 14th World Congress on Pain (August 27-31, 2012), [PF 012], available through http://www.abstracts2view.com/iasp/ and attached as Exhibit 2; Coplan, P. *et al., Effects of reformulated OxyContin® on opioid abuse in the National Poison Data System,* American Pain Society, 31st Annual Scientific Meeting (May 16-19, 2012), Abstract ID # 464 and Poster # 430, available at: http://www.ampainsoc.org/abstract/2012/view/5203/ and attached as Exhibit 3.

NPDS also provides information on rates adjusted by 100,000 population and by 100 prescriptions.[36] The estimated rate per 100,000 population for all OxyContin exposures declined 23% in the post-period compared to the pre-period, intentional exposures declined 20%, intentional abuse exposures declined 31%, unintentional exposures declined 24%, therapeutic errors among patients declined by 18%, and unintentional general exposures declined by 39%.

The effects were diminished when adjusted by the number of prescriptions: the estimated rate for all OxyContin exposures declined 7% in the post-period compared to the pre-period, intentional exposures declined 3%, intentional abuse exposures declined 17%, unintentional exposures declined 9%, therapeutic errors among patients declined by 2%, and unintentional general exposures declined by 26%. As explained above, these adjusted rates underestimate the impact of the reformulation because the adjustment factor (*i.e.*, prescriptions dispensed) does not reflect the continued widespread availability of original OxyContin through illicit channels.

(b) Law Enforcement Events Reported in the Drug Diversion Program of the RADARS® System

The RADARS® System Drug Diversion ("DD") Program provides systematic surveillance data on prescription drug diversion. Diversion events estimate the demand of prescription opioids for abuse via illegal networks across the United States.

Law enforcement officials and regulatory agencies serve as reporters by completing the National Drug Diversion Survey and Street Price Questionnaires on a quarterly basis. These questionnaires elicit information on the number of new cases of diversion and on the street price of specific diverted products. The DD Program surveys approximately 300 reporters in all 50 states.

The DD Program collects information on diversion of specific drug products, but does not distinguish between original OxyContin and reformulated OxyContin. DD survey data on extended release ("ER") oxycodone have been collected on an ongoing basis since the first quarter of 2002, providing an extensive baseline against which to compare trends before and after launch of reformulated OxyContin. For purposes of the latest published reports of this study, October 1, 2008 through September 30, 2010 was considered the period before introduction of reformulated OxyContin and the period from

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[36] Coplan, P. *et al., National Changes in OxyContin, other Oxycodone, and Heroin Exposures Reported to Poison Centers with Introduction of Reformulated OxyContin®*, 74th Annual Scientific Meeting of the College on Problems of Drug Dependence, Poster # 71 (presented June 13, 2012), at Table 1, attached as Exhibit 1.

October 1, 2010 to December 30, 2011 was considered the period after introduction of reformulated OxyContin.[37]

To adjust for changes over time in the RADARS® program coverage, diversion rates per 100,000 population were calculated. To adjust for changes in drug availability, diversion rates per 1,000 unique recipients of dispensed drug ("URDD") were calculated. The average OxyContin diversion population rate in the after period is 51% (95% CI: 37 to 61%, $p<0.001$) less than the average population rate in the before period. There was an estimated 49% (95% CI: 36 to 59%, $p<0.001$) decline in the average OxyContin diversion URDD rate in the after-period compared to the before period. The differences in the population and URDD rates for opioids other than OxyContin, were not significant, indicating that the observed decline in OxyContin diversion rates was not reflective of an overall change in diversion of prescription opioids.

(c) Street Price Data Reported in the Drug Diversion Program of the RADARS® System

In addition to providing estimates of diversion, the RADARS® DD program provides information on the cost of diverted products on the street -- another marker of product desirability for abuse. The Street Price questionnaires completed by participating law enforcement officials and regulatory agencies elicit information on the street price of specific diverted products – differentiating between original and reformulated OxyContin. Three references analyzing RADARS® street price data have been published, each comparing prices during slightly different time periods, and each finding the street price for reformulated OxyContin to be substantially less than the street price for the original formulation of OxyContin.

For example, an analysis of prices between the first quarter of 2010 and the third quarter of 2011, excluding the second quarter of 2010, shows that the geometric mean street price of original OxyContin was $0.80 per milligram before launch of reformulated

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[37] Severtson, S. *et al. Reduction in OxyContin® diversion cases following the introduction of reformulated OxyContin,* 74th Annual Scientific Meeting of the College on Problems of Drug Dependence, Abstract # 611, available through http://www.cpdd.vcu.edu/Pages/Meetings/CPDD12AbstractBook.pdf and Poster # 70 (presented June 13, 2012), attached collectively as Exhibit 6 (latest data provided in the Poster). *See also* Severtson, S. G., *et al., Reduced Abuse and Diversion Following the Reformulation of OxyContin®,* RADARS® System 6th Annual Meeting (April 24, 2012), available at: http://www.radars.org/Portals/1/OxyContin_ADF_Poster_20120424_FINAL.pdf and attached as Exhibit 5. An additional analysis of these data covering a different time period is described at Davis, J. *et al., Reduction in Extended Release (ER) Oxycodone Diversion Rates Following The Introduction of A Reformulated ER Oxycodone Product,* International Association for the Study of Pain, 14th World Congress on Pain (August 27-31, 2012), [PF 087], available through http://www.abstracts2view.com/iasp/ and attached as Exhibit 7.

OxyContin and $0.85 after launch. The geometic mean price of reformulated OxyContin was $0.68 per milligram, which is 21% lower than the original formulation of OxyContin in the period after introduction of reformulated OxyContin.[38]

An analysis through the fourth quarter of 2011 reports a statistically significant 9% price increase for the original formulation of OxyContin, from $0.81 per milligram before launch of reformulated OxyContin to $0.89 after launch. In this analysis, the geometic mean street price per milligram of the reformulation was $0.69, which is 22% lower than the original formulation in the period after introduction of reformulated OxyContin.[39]

A third reference reports street prices for original and reformulated OxyContin similar to those reported above, with the price of the reformulation 18.8% lower than the street price of original OxyContin following launch of reformulated OxyContin. In addition, the geometic mean street price for immediate release oxycodone increased 16.6% following introduction of reformulated OxyContin.[40]

(d) OxyContin Abuse Among Patients in Substance Abuse Treatment Programs in the ASI-MV® Connect NAVIPPRO™ System

This study was designed to assess both differences in abuse of reformulated OxyContin via routes of administration that require tampering and differences in rates of abuse of reformulated OxyContin, compared to original OxyContin in the period prior to launch of reformulated OxyContin. Data were collected from a sample of substance abuse treatment centers in the United States using the NAVIPPRO® Addiction Severity Index-Multimedia Version (ASI-MV®) system. The ASI-MV is a standard intake assessment designed for use on admission to drug and alcohol treatment which contains questions about past-30-day abuse of prescription medications, with product-specific questions about routes of administration. Identification of specific medications is determined by presenting images along with audio of medication names, slang names,

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[38] Bucher-Bartelson, B. *et al., A Comparison Of The Street Price Of Original And Reformulated ER Oxycodone,* International Association for the Study of Pain, 14th World Congress on Pain (August 27-31, 2012), [PF 085], available through http://www.abstracts2view.com/iasp/ and attached as Exhibit 8.

[39] Severtson, S. G., *et al., Reduced Abuse and Diversion Following the Reformulation of OxyContin®,* RADARS® System 6th Annual Meeting (April 24, 2012), available at: http://www.radars.org/Portals/1/OxyContin_ADF_Poster_20120424_FINAL.pdf and attached as Exhibit 5.

[40] Severtson, S. *et al., A comparison of the street price of original and reformulated OxyContin® and immediate release (IR) oxycodone products,* American Pain Society, 31st Annual Scientific Meeting (May 16-19, 2012), Abstract ID # 446 and Poster # 201, available at: http://www.ampainsoc.org/abstract/2012/view/4977/ and attached as Exhibit 9.

and street names. Historical rates and routes of administration of original OxyContin were measured over the 14 months preceding launch of reformulated OxyContin (the before-period), and compared with data on reformulated OxyContin in up to 20 months following launch on August 9, 2010 (the after-period).[41]

In the before-period, there were 60,002 total assessments; in the after-period, there were 71,494 total assessments. Of the 140,496 individuals assessed in both periods combined, 26,453 (18.8%) reported abuse of at least one prescription opioid in the 30 days preceding assessment.

3.0% of the entire before-sample reported abuse of original OxyContin through non-oral routes of administration while 1.0% of the after-sample reported abuse of reformulated OxyContin through non-oral routes of administration. Rates for oral route of administration also decreased from 2.1% for original OxyContin in the before period versus 1.8% for reformulated OxyContin in the after period.[42] A similar pattern of

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[41] Several published abstracts and posters report on these data. The most current data are available in posters presented at the 74th Annual Scientific Meeting of the College on Problems of Drug Dependence. *See* Cassidy, T., *et al., Change in routes of administration for OxyContin and comparators following introduction of reformulated OxyContin® among individuals assessed for substance abuse,* 74th Annual Scientific Meeting of the College on Problems of Drug Dependence, Abstract # 88, available through http://www.cpdd.vcu.edu/Pages/Meetings/CPDD12AbstractBook.pdf and Poster # 66 (presented June 13, 2012), attached collectively as Exhibit 11; Chilcoat, H., *et al., Impact of reformulated OxyContin® on rates of abuse through oral and non-oral routes among individuals assessed in substance abuse treatment,* 74th Annual Scientific Meeting of the College on Problems of Drug Dependence, Abstract # 103, available through http://www.cpdd.vcu.edu/Pages/Meetings/CPDD12AbstractBook.pdf and Poster # 68 (presented June 13, 2012), attached collectively as Exhibit 10.

Additional published reports on this study covering different time periods are also enclosed. *See* Butler, S., *et al., Differences in Rates of Abuse and Routes of Administration for Original and Reformulated extended-release oxycodone among individuals assessed for substance abuse,* International Association for the Study of Pain, 14th World Congress on Pain (August 27-31, 2012), [PF 010], available through http://www.abstracts2view.com/iasp/ and attached as Exhibit 12; Black, R. *et al., Effects of reformulated OxyContin® among patients assessed for substance abuse treatment in the NAVIPPRO sentinel surveillance network,* American Pain Society, 31st Annual Scientific Meeting (May 16-19, 2012), Abstract ID # 490 and Poster # 331, available at: http://www.ampainsoc.org/abstract/2012/view/5104/ and attached as Exhibit 13; Butler, S., *et al., Initial findings on abuse rates and routes of administration among individuals assessed for substance use treatment following introduction of reformulated OxyContin®,* 2nd Annual NAVIPPRO® Scientific Meeting, *A Comprehensive System for Prescription Drug Abuse Surveillance and Intervention – New Findings, New Directions,* (March 28, 2012), available at: http://www.navippro.com/uploadedFiles/NAVIPPRO_ReformulationOxyContin.pdf and attached as Exhibit 14; Cassidy, T.A., *et al., Initial findings on abuse rates and routes of administration following introduction of reformulated OxyContin® (oxycodone HCL controlled-release) Tablets in a sentinel surveillance system of patients in substance use treatment,* PainWeek (Sept. 7-20, 2011), Abstract # 13 available at: http://www.painweek.org/media/mediafile_attachments/05/255-13.pdf and Poster, attached collectively hereto as Exhibit 15.

[42] Cassidy, T., *et al., Change in routes of administration for OxyContin and comparators following introduction of reformulated OxyContin® among individuals assessed for substance abuse,* 74th Annual

findings was observed when the sample was restricted to those who reported abuse of at least one opioid.[43]

Among those who abused OxyContin, the percent reporting injecting decreased from 35.7% for original OxyContin in the before-period to 15.9% for reformulated OxyContin in the after-period; snorting reduced from 52.7% to 25.4%, and smoking reduced from 6.4% to 4.2%. Because this route-of-administration-specific analysis was restricted to only those who abused OxyContin (through any route), the reduction in the non-oral route rates was accompanied by a corresponding increase in the percentage of oral abuse, although the lower rate of oral abuse of reformulated OxyContin among all respondents indicates that fewer respondents were abusing reformulated OxyContin orally in the after period, compared to oral abuse of original OxyContin in the before period.[44]

Abuse of original OxyContin also persisted in the after-period and is not reflected in the above-referenced data. A separate poster presentation examining rates of abuse includes data on abuse of original OxyContin in the after period. In particular, after introduction of reformulated OxyContin, abuse of original OxyContin continued to be reported, but those reports declined over time, likely due to decreasing availability of original OxyContin. Prevalence of abuse of reformulated OxyContin reached a steady level soon after its introduction, and has not increased as abuse of original OxyContin has declined.[45] Overall, the rate of abuse of reformulated OxyContin during the first 20 months following its introduction was significantly lower than the rate of abuse for original OxyContin in the period prior to launch of reformulated OxyContin. All

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Scientific Meeting of the College on Problems of Drug Dependence, Abstract # 88, available through http://www.cpdd.vcu.edu/Pages/Meetings/CPDD12AbstractBook.pdf and Poster # 66 (presented June 13, 2012), attached collectively as Exhibit 11.

[43] Black, R. *et al., Effects of reformulated OxyContin® among patients assessed for substance abuse treatment in the NAVIPPRO sentinel surveillance network,* American Pain Society, 31st Annual Scientific Meeting, Abstract ID # 490 and Poster # 331, available at: http://www.ampainsoc.org/abstract/2012/view/5104/ and attached as Exhibit 13.

[44] Cassidy, T., *et al., Change in routes of administration for OxyContin and comparators following introduction of reformulated OxyContin® among individuals assessed for substance abuse,* 74th Annual Scientific Meeting of the College on Problems of Drug Dependence, Abstract # 88, available through http://www.cpdd.vcu.edu/Pages/Meetings/CPDD12AbstractBook.pdf and Poster # 66 (presented June 13, 2012), attached collectively as Exhibit 11.

[45] Chilcoat, H., *et al., Impact of reformulated OxyContin® on rates of abuse through oral and non-oral routes among individuals assessed in substance abuse treatment,* 74th Annual Scientific Meeting of the College on Problems of Drug Dependence, Abstract # 103, available through http://www.cpdd.vcu.edu/Pages/Meetings/CPDD12AbstractBook.pdf and Poster # 68 at Figure 1 (presented June 13, 2012), attached collectively as Exhibit 10.

outcome measures for this study showed lower rates of abuse for reformulated OxyContin in the after period, compared to original OxyContin in the before period, including: rates among all participants assessed for abuse, rates among those participants assessed for abuse who reported abusing opioids, rates of abuse adjusted for prescribed availability, rates through oral and non-oral routes, and the number of days of abuse in the past 30 days.[46]

(e) Changes in Abuse Patterns in a Cohort of People Abusing OxyContin in Rural Kentucky

This study examined the patterns of abuse of OxyContin as well as other opioids before and after the introduction of reformulated OxyContin in a cohort of individuals in eastern Kentucky who had abused the original formulation of OxyContin prior to the introduction of reformulated OxyContin. Past as well as current substance use patterns were examined, including type, amount, method and route of administration of pharmaceutical opioid drugs, as well as illicit drugs.[47]

A total of 192 individuals who were abusing OxyContin prior to the introduction of reformulated OxyContin in August 2010 were recruited from rural Perry County, in the Appalachian region of Kentucky; 189 were included in the final analysis. An interviewer-administered questionnaire was used to determine the subjects' history of substance use/abuse in addition to demographics, employment, medical history, and psychiatric history. Substances assessed included: alcohol, heroin, licit methadone, illicit methadone, licit buprenorphine, illicit buprenorphine, OxyContin, other oxycodone, other pharmaceutical opioids (fentanyl, hydromorphone), barbiturates, benzodiazepines, cocaine, crack, methamphetamine, and marijuana. To examine substance use, participants were asked whether they have ever used the substance, use in past 30 days as well as in the month prior to introduction of reformulated OxyContin, age at first use, and source of the drug.

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46 *Id.*

47 DeVeaugh-Geiss, A. *et al., Routes of administration and frequency of abuse of OxyContin® and immediate-release oxycodone in a rural Kentucky county following introduction of reformulated OxyContin,* 74th Annual Scientific Meeting of the College on Problems of Drug Dependence, Abstract # 146, available through http://www.cpdd.vcu.edu/Pages/Meetings/CPDD12AbstractBook.pdf and Poster # 65 (presented June 13, 2012), collectively attached as Exhibit 16. The original Abstract posted on the CPDD website reflects some inaccuracies that were identified upon reanalysis of the raw data. The corrected data are included in the Poster presented June 13, 2012 at the CPDD conference.

An additional abstract and poster report on this study. *See* Leukefeld, C. *et al., Changes in Prescription and OxyContin® Drug Abuse Patterns in a Rural Kentucky County,* 74th Annual Scientific Meeting of the College on Problems of Drug Dependence, Abstract # 358, available through http://www.cpdd.vcu.edu/Pages/Meetings/CPDD12AbstractBook.pdf and Poster # 69 (presented June 13, 2012), collectively attached as Exhibit 17.

Participants were asked about their methods of preparation and the routes of administration for all pharmaceutical and illegal opioids during the past 30 days (prior to interview) and during the month of August 2010. To anchor these questions about use prior to introduction of reformulated OxyContin, participants were asked about abuse at the time of an event that is well known in the area called "Black Gold." The timing of the Black Gold festival coincided with the launch of reformulated OxyContin in August 2010.

Abuse of original OxyContin continued after launch of reformulated OxyContin despite lack of availability through legal channels, though the prevalence of abuse declined over time.

Before launch of reformulated OxyContin, original OxyContin was abused by 2% of this study population by swallowing, 39% by snorting, and 41% by injecting. After its introduction, abuse of reformulated OxyContin was mainly limited to swallowing, with 22% reporting swallowing, 5% snorting, and only one participant reporting injecting. The frequency of abuse of OxyContin among those who abused through each route was: swallowing: average 4.0 days per month for original OxyContin before launch of reformulated OxyContin and average 6.8 days per month for reformulated OxyContin; snorting: 15.2 days for original OxyContin and 4.2 days for reformulated OxyContin; injecting: 20.8 days for original OxyContin and 1.0 day for reformulated OxyContin.

Prevalence of immediate release oxycodone abuse increased in this study population in the period following launch of reformulated OxyContin, from 9% to 29% for swallowing, 46% to 69% for snorting, and 31% to 51% for injecting. Frequency of immediate release oxycodone abuse increased for injecting ROA (18.4 to 20.4 days) and decreased slightly for swallowing (14.7 to 12.6 days) and snorting (15.9 to 14.7 days).

(f) Summary of Epidemiologic Study Results

Select findings from the epidemiologic studies described in Sections (a) through (e) above are provided in the following table. Information on study methodology and additional study findings are described in Sections (a) through (e) above and in the abstracts and posters attached to this Petition and referenced in the table.

Study	Select Findings	Primary Exhibit Reference	Additional Exhibit References
Poison Center (RADARS®)	Data show an estimated 34% decline in the average abuse rate per 100,000 population and an estimated 29% decline in the average abuse rate per 1,000 URDD after the introduction of reformulated OxyContin.	5	4

	These declines were greater than the changes observed for opioids other than OxyContin.		
Poison Center (NPDS)	All OxyContin exposures declined 22% in the post-period compared to the pre-period. Similarly, intentional exposures declined 19% and intentional abuse exposures (a subset of intentional exposures) declined 30% . Unintentional exposures declined 20% in the post-period compared to the pre-period and therapeutic errors among patients (a subset of unintentional exposures) by 17%. The effects were diminished when adjusted by the number of prescriptions.	1	2, 3
Drug Diversion (RADARS)	There was an estimated 51% decline in the average OxyContin diversion population rate and an estimated 49% decline in the average OxyContin diversion URDD rate in the period after launch of reformulated OxyContin, compared to the period before launch.	6	5, 7
Street Price (RADARS)	The geometric mean street price of original OxyContin was $0.80 per mg before launch of reformulated OxyContin and rose to $0.85 after launch. The price of reformulated OxyContin was $0.68 per mg, which is 21% lower than the original formulation in the period after launch of the reformulation.	8	5, 9
NAVIPPRO	Among those who abused OxyContin, the percent reporting injecting decreased from 35.7% for original OxyContin in the before-period to 15.9% for reformulated OxyContin in the after-period; snorting reduced from 52.7% to 25.4%, and smoking reduced from 6.4% to 4.2%, respectively.	10, 11	12-15
Kentucky	Before launch of reformulated OxyContin, original OxyContin was abused by 2% of this study population by swallowing, 39% by snorting, and 41% by injecting. After its introduction, abuse of reformulated OxyContin was mainly limited to swallowing, with 22% reporting swallowing, 5% snorting, and only one participant reporting injecting. The frequency of abuse of OxyContin among those who abused through each route was:	16	17

	swallowing: average 4.0 days per month for original OxyContin before launch of reformulated OxyContin and average 6.8 days per month for reformulated OxyContin; snorting: 15.2 days for original OxyContin and 4.2 days for reformulated OxyContin; injecting: 20.8 days for original OxyContin and 1.0 day for reformulated OxyContin.		

6. Pharmacokinetic and Abuse Potential Studies of Reformulated OxyContin

Data from four clinical studies of reformulated OxyContin have also been made available publicly in abstracts and posters submitted for the 74th Annual Scientific Meeting of the College on Problems of Drug Dependence, June 9-14, 2012. 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 below and in the attached abstracts and posters.[48]

(a) Evaluation of Abuse Potential of Crushed and Intranasally Administered Oxycodone Tablets[49]

Recreational opioid users were exposed to 30 milligrams of oxycodone administered intranasally in the form of coarsely crushed reformulated OxyContin, finely crushed reformulated OxyContin, crushed original OxyContin, oxycodone API powder,

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[48] Study results report on a number of pharmacokinetic and pharmacodynamic parameters. The following explanation is included for the convenience of the reader. C_{max} refers to the maximum (or peak) concentration of a drug observed after its administration. T_{max} refers to the time after administration of a drug when C_{max} is reached. Area under the curve (AUC) refers to the area under the plot of plasma concentration of drug against time after drug administration. AUC_t and AUC_{inf} are two means of expressing total exposure following administration of a drug. AUC_t refers to the observable exposure and is the area under the plasma concentration of drug against time curve from time zero to time t, where t is the last time point with measurable concentration for individual formulation. AUC_{inf} refers to the complete exposure and is the area under the plasma concentration of drug against time curve from time zero to infinity, which must be extrapolated from measured exposure. E_{max} refers to the maximum response that can be produced by a drug, after which increases in drug concentrations will not result in corresponding increases in pharmacological response.

[49] Perrino, P. *et al.* 74th Annual Scientific Meeting of the College on Problems of Drug Dependence, Abstract # 522, available through http://www.cpdd.vcu.edu/Pages/Meetings/CPDD12AbstractBook.pdf and Oral Presentation (presented June 13, 2012), collectively attached as Exhibit 18.

and placebo in a randomized, double-blind, crossover study. Administration of reformulated OxyContin (coarse and fine) resulted in reduced and delayed peak oxycodone concentrations compared to crushed original OxyContin and oxycodone API powder. Peak effects for subjective measures (visual analog scales ("VAS") for Drug Liking, Take Drug Again, and High) and pupillometry occurred later for reformulated OxyContin compared with original OxyContin and oxycodone API. Peak VAS (E_{max}) values were greatest for oxycodone API and crushed original OxyContin, and lower for reformulated OxyContin (fine and coarse) and placebo. Subjective Drug Value ratings were highest for oxycodone API and crushed original OxyContin, and lower for reformulated OxyContin (fine and coarse) and placebo. Abuse quotient ("AQ"), calculated as C_{max}/T_{max}, was highest for oxycodone API and original OxyContin. Coarse and fine crushed reformulated OxyContin AQs were approximately 83% lower than oxycodone API. Reformulated OxyContin was associated with higher E_{max} on measures of intranasal irritation compared to original OxyContin and oxycodone API.

(b) Safety, Tolerability, and Pharmacokinetics of Crushed Intranasal Oxycodone Tamper Resistant Tablets and OxyContin® in Healthy Adults[50]

Finely and coarsely crushed reformulated OxyContin and finely crushed original OxyContin were administered intranasally to healthy adults in a randomized, single-blind, single-dose, 3-treatment, 3-period crossover study. The three treatments were bioequivalent measured by total exposure (AUC_t and AUC_{inf}). In contrast to the original formulation of OxyContin, both finely and coarsely crushed reformulated OxyContin retained some control of oxycodone release after intranasal administration. C_{max} values for reformulated OxyContin (fine and coarse) were lower than original OxyContin; none of the treatment comparisons met the bioequivalence criterion for C_{max}. T_{max} for original OxyContin occurred more rapidly than for reformulated OxyContin (fine and coarse). Abuse Quotient (AQ), calculated as C_{max}/T_{max}, was highest for original OxyContin. Coarse and fine crushed reformulated OxyContin AQs were approximately 80% and 66% lower, respectively, than finely crushed original OxyContin. Administration of reformulated OxyContin resulted in statistically significantly greater nasal discomfort and stuffiness compared to original OxyContin, while the latter produced higher runny nose scores, compared to reformulated OxyContin.

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[50] Colucci, S. *et al.*, 74th Annual Scientific Meeting of the College on Problems of Drug Dependence, Abstract # 114, available through http://www.cpdd.vcu.edu/Pages/Meetings/CPDD12AbstractBook.pdf and Poster # 79 (presented June 12, 2012), attached collectively as Exhibit 19.

(c) Effects of Various Tampering Methods on Exposure to Oxycodone in Healthy Subjects[51]

Pharmacokinetic parameters were evaluated after oral administration of 40 mg oxycodone in the form of immediate-release oxycodone solution, intact reformulated and original OxyContin tablets, and reformulated and original OxyContin subjected to various tampering methods. Compared to original OxyContin, reformulated OxyContin demonstrated improved resistance to manipulations intended to disrupt the control of oxycodone release. Total oxycodone exposure (AUC) was equivalent for immediate-release oxycodone solution and intact and tampered reformulated OxyContin and original OxyContin. Particle size reduction of reformulated OxyContin by mortar and pestle did not affect the control of oxycodone release. Under both normal and vigorous chewing conditions, the control of oxycodone release from original OxyContin was completely defeated, while reformulated OxyContin retained some control of oxycodone release (lower C_{max} and higher T_{max}). In particular, following vigorous chewing, the median C_{max} was 13.5% lower, and the median T_{max} was 50% higher, for reformulated OxyContin compared to original OxyContin. Under normal chewing conditions, the median C_{max} was 23.6% lower, and the median T_{max} 111% higher, for reformulated OxyContin compared to original OxyContin. Abuse quotient ("AQ"), calculated as C_{max}/T_{max}, was highest for immediate-release oxycodone solution and chewed original OxyContin. Chewed reformulated OxyContin AQ values were 23 – 37% lower than the AQ for immediate-release oxycodone solution. Following vigorous and normal chewing, the AQ values for ORF were statistically significantly lower ($p \leq 0.03$) than the AQs for chewed original OxyContin.

(d) Relative Attractiveness of Reformulated OxyContin®: Comparative Assessment of Tampering Potential and Recreational Drug User Preferences for Opioid Formulations[52]

In this non-interventional, single-session study, Canadian subjects experienced in tampering with prescription formulations were presented with seven oxycodone-containing products in a randomized fashion using information cards. Subjects were also given the opportunity to tamper with reformulated OxyContin and original OxyContin

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[51] Harris, S. *et al.*, 74th Annual Scientific Meeting of the College on Problems of Drug Dependence, Abstract # 242, available through http://www.cpdd.vcu.edu/Pages/Meetings/CPDD12AbstractBook.pdf and Poster # 78 (presented June 12, 2012), attached collectively as Exhibit 20 (updated data provided in Poster).

[52] Sellers, E. *et al.*, 74th Annual Scientific Meeting of the College on Problems of Drug Dependence, Abstract # 605, available through http://www.cpdd.vcu.edu/Pages/Meetings/CPDD12AbstractBook.pdf and Poster # 72 (presented June 13, 2012), attached collectively as Exhibit 21.

placebo tablets using commonly available supplies (*e.g.*, hammer, pill crusher, mortar and pestle, and X-Axto™ knife). Subjects responded to questions about the products and their tampering potential. Original OxyContin had the highest mean score on the Opioid Attractiveness Scale, while a hypothetical oxycodone/naltrexone oral product and reformulated OxyContin ranked the lowest. Original OxyContin ranked highest on Overall Desirability and Estimated Street Value, while reformulated OxyContin was ranked second to last, just above a hypothetical oxycodone/naltrexone oral product.

B. Statutory and Regulatory Background Concerning Generic Drugs

In 1984, Congress enacted the Drug Price Competition and Patent Term Restoration Act of 1984 ("Hatch-Waxman Amendments"), which created an approval pathway for generic versions of approved innovator drug products, such as OxyContin. Generic drugs are intended to be, and described by FDA and other government agencies as, essentially copies of already-approved innovator drugs that have been shown through clinical trials to be safe and effective. FDA and other agencies have further assured the public that generic drugs are as safe and effective as the innovator drugs they copy. In the words of FDA:

> [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. Health care professionals and consumers can be assured that FDA approved generic drug products have met the same rigid standards as the innovator drug. All generic drugs approved by FDA have the same high quality, strength, purity and stability as brand-name drugs.[53]

Similarly, the Agency has explained the relationship between generic and innovator drugs as follows:

> Generics use the same ingredients, and
> - work the same in the body
> - have the same risk-benefit profile[54]

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[53] *Understanding Generic Drugs,* available at: http://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/UnderstandingGenericDrugs/default.htm (emphasis supplied).

[54] 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 (emphasis supplied).

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Generic Drugs

A generic drug is a chemical clone of a drug sold under a brand name.[55]

Other consumer education pieces explain that generic drugs are as safe as their brand name counterparts:

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.[56]

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FACT: FDA requires generic drugs to have the same quality and performance as the brand name drugs.[57]

In another similar piece FDA assures the public that generic drugs must meet the same quality and safety standards as brand name drugs:

What is a generic drug?

When a brand-name drug's patent protection expires, generic versions of the drug can be approved for sale. The generic version works like the brand-name drug in dosage, strength, performance and use, and must meet the same quality and safety standards. All generic drugs must be reviewed and approved by FDA.[58]

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[55] CDER: The Consumer Watchdog for Safe and Effective Drugs, available at: http://www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm143462.htm (emphasis supplied).

[56] Facts about Generic Drugs, available at: http://www.fda.gov/downloads/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/UnderstandingGenericDrugs/UCM219406.pdf (emphasis supplied).

[57] Facts and Myths about Generic Drugs, available at: http://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/UnderstandingGenericDrugs/ucm167991.htm (emphasis supplied).

[58] 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:

The Federal Trade Commission promotes these same messages through its own public education campaign:

> Generic drugs are as effective and safe as the brand-name drugs they're based on. They have the same active ingredients and must work the same way as their brand-name counterparts to be approved by the FDA. That means they have the same risks and benefits, too. [59]

The Centers for Medicare and Medicaid Services also publicize this same type of information, assuring the public that generic drugs perform in the same way as the brand name drug products they copy:

> The Food and Drug Administration (FDA) says a generic drug is the same as its brand-name counterpart in safety, strength, quality, the way it works, how it's taken, and the way it should be used. Generic drugs use the same active ingredients as brand-name drugs. Generic drug makers must prove to the FDA that their product performs the same way as the corresponding brand-name drug.[60]

Through the approval pathway created as part of the Hatch-Waxman Amendments, a company seeking to market a generic copy of a previously-approved drug may file an abbreviated new drug application ("ANDA") with FDA. 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 previously-approved drug ("Reference Listed Drug" or "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 Reference Listed Drug. 21 U.S.C. § 355(j)(2)(A). 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

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http://www.fda.gov/downloads/Drugs/EmergencyPreparedness/BioterrorismandDrugPreparedness/UCM133888.pdf (emphasis supplied).

[59] 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. *See also* 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 (emphasis supplied).

[60] 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 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.

administration, and labeling as the Reference Listed Drug, as well as information showing that the generic product is bioequivalent to the RLD. 21 U.S.C. § 355(j)(2)(A). Upon making the statutorily required showings, the generic applicant may piggyback upon FDA's previous finding that the RLD is safe and effective, based on the extensive preclinical and clinical data submitted for the Reference Listed Drug. The purpose of these provisions "is to assure the marketing of generic drugs that are as safe and effective as their brand-name counterparts."[61]

Both the statute and FDA regulations identify a variety of conditions under which FDA may not approve an ANDA. Four of these conditions are particularly relevant to Agency consideration of an application seeking approval to market a generic version of reformulated OxyContin:

(1) FDA may not approve an ANDA if information submitted in the application is insufficient to show that the dosage form is the same as that of the RLD. 21 U.S.C. § 355(j)(4)(D); 21 C.F.R. § 314.127(a)(4).

(2) FDA may not approve an ANDA if information submitted in the application is insufficient to show that the drug is bioequivalent to the RLD referred to in the application. 21 U.S.C. § 355(j)(4)(F); 21 C.F.R. § 314.127(a)(6).

(3) FDA may not approve an ANDA if information submitted in the application is insufficient to show that the labeling proposed for the generic drug is the same as the labeling approved for the RLD. 21 U.S.C. § 355(j)(4)(G); 21 C.F.R. § 314.127(a)(7).

(4) FDA may not approve an ANDA if information submitted in the application or any other information available to the Secretary 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).

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[61] *Abbreviated New Drug Application Regulations; Proposed Rule,* 54 Fed. Reg. 28872, 28879 (July 10, 1989) (emphasis supplied).

C. Argument

1. Generic Versions of OxyContin Must be Shown to Perform As Well As Reformulated OxyContin Under Conditions Designed to Simulate Tampering

Last year, the White House identified prescription drug abuse as an "epidemic" that is "the nation's fastest growing drug problem."[62] On April 19, 2011, the Obama Administration announced a comprehensive action plan to address prescription drug abuse, focusing primarily on abuse of prescription opioids.[63] The Action Plan addresses abuse deterrent formulations, stating that FDA intends to issue a "guidance document on developing abuse deterrent drug formulations and on post-market assessment of their performance within 24 months."[64] Congress too has urged FDA action to encourage development and prompt approval of such formulations.[65]

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[62] 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; *Epidemic: Responding to America's Prescription Drug Abuse Crisis* (April 2011), at p. 1, available at: http://www.whitehouse.gov/sites/default/files/ondcp/issues-content/prescription-drugs/rx_abuse_plan.pdf.

[63] In support of the White House action plan, FDA is requiring a Risk Evaluation and Mitigation Strategy (REMS) for all long-acting and extended-release opioids. The new program, approved July 9, 2012, requires manufacturers of these products to provide educational programs to prescribers of these medications, as well as materials prescribers can use when counseling patients about the risks and benefits of opioid use. *See* FDA introduces new safety measures for extended-release and long-acting opioid medications, available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm310870.htm; Risk Evaluation and Mitigation Strategy (REMS) for Extended-Release and Long-Acting Opioids, available at: http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm163647.htm; Questions and Answers: FDA approves a Risk Evaluation and Mitigation Strategy (REMS) for Extended-Release and Long-Acting (ER/LA) Opioid Analgesics, available at: http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm309742.htm.

[64] *Epidemic: Responding to America's Prescription Drug Abuse Crisis* (April 2011), at p. 10, available at: http://www.whitehouse.gov/sites/default/files/ondcp/issues-content/prescription-drugs/rx_abuse_plan.pdf.

[65] Congress has addressed these issues in appropriations reports. *See, e.g.,* Senate Report 109-266 (June 22, 2006) at p. 142 ("*Expedited filing* – The Committee directs FDA to expedite and support the filing, review and final action on new drug applications or a supplement to a new drug application seeking approval of a reformulated active ingredient, or combination of active ingredients, previously approved as safe and effective that would replace or provide a therapeutic alternative to a currently marketed drug product that contains an active ingredient that is the subject of diversion and/or abuse outside regulated channels of commerce"); H.R. 109-255 (Oct. 26, 2005), at p. 102 ("The conferees note that FDA may use

Though there have long been calls for development of "abuse resistant" opioids to help combat this problem, and many companies have undertaken development efforts, few products specifically formulated to discourage abuse and misuse are commercially available. The relative dearth of such formulations is attributable in large part to the significant technical challenges presented by the task of developing a formulation that provides effective pain relief when taken as directed by patients, but that incorporates effective impediments to abuse or misuse. Reformulated OxyContin is one of only a few such approved products. The first three such products approved by FDA include both an opioid agonist and an opioid antagonist intended to discourage misuse and abuse under certain conditions. In August 2009, FDA approved the NDA for Embeda® (morphine sulfate; naltrexone hydrochloride) Extended Release Capsules.[66] Suboxone® (buprenorphine hydrochloride; naloxone hydrochloride) sublingual tablets was approved in October 2002, while the sublingual film dosage form of Suboxone® was approved in

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available funds to support review and action on new drug applications and supplements seeking approval for replacement or alternative abuse-resistant formulations of currently-available drug products that include an active ingredient that is a listed chemical under the Controlled Substances Act. Further, it is the understanding of the conferees that these applications may be considered under the expedited, priority review process at FDA"); H.R. 109-102 (June 2, 2005), at p. 81 ("*Abuse of Prescription Drugs* – The Committee is interested in the potential benefit from FDA's development of procedures for approval of abuse-resistant formulations of schedule II painkillers and other prescription drugs currently on the market. The Committee notes that FDA priority review can be granted in cases in which the drug product 'would be a significant improvement compared to marketed products . . . in the treatment, diagnosis, or prevention of a disease' including 'elimination or substantial reduction of a treatment-limiting drug reaction'. The Committee requests FDA to report on whether a drug less prone to abuse would be considered under that provision, and if so, how many drugs were considered under the provision due to less potential for abuse, and granted priority status. Additionally, FDA should take all appropriate steps to ensure that health care providers and patients are given all relevant information concerning the abuse-resistant qualities of safer drugs. Providers and patients alike will benefit from the expedited review of safer drugs, as well as the provision of information that accurately differentiates abuse-resistant formulations").

[66] According to the sponsor, "EMBEDA® is expected to deter abuse by chewing and swallowing, crushing and snorting or dissolving and injecting, as these forms of tampering will also release the sequestered opioid antagonist naltrexone blunting the psychoactive effects of morphine." *See* Joint Anesthetic and Life Support Drugs (ALSDAC) and Drug Safety and Risk Management (DSaRM) Advisory Committee Briefing Document, EMBEDA® Extended Release Capsules, Meeting Date: 21-22 October 2010, Alpharma Pharmaceuticals LLC, a subsidiary of King Pharmaceuticals, Inc. at p. 5, available at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndLifeSupportDrugsAdvisoryCommittee/UCM230111.pdf. The Embeda website currently states: "King Pharmaceuticals Inc., a wholly owned subsidiary of Pfizer, has voluntarily recalled from U.S. wholesalers and retailers all dosage forms of EMBEDA® (morphine sulfate and naltrexone hydrochloride) Extended Release Capsules CII because a pre-specified stability requirement was not met during routine testing." *See* www.embeda.com.

August 2010. The NDA for Talwin® Nx (Pentazocine Hydrochloride; Naloxone Hydrochloride) tablets was approved in December 1982.

Unlike these three previously approved products, OxyContin does not contain an opioid antagonist, but instead contains an inert excipient that changes the physicochemical properties of the tablets in a manner intended to discourage abuse and misuse. Most recently, FDA approved two additional products designed to discourage misuse and abuse: Oxecta™ (oxycodone hydrochloride) Tablets, an immediate release oxycodone product, was approved on June 17, 2011,[67] and a new formulation of Opana® ER, an extended release oxymorphone product designed to be crush-resistant, was approved on December 9, 2011.[68] NDAs for other products formulated with the intention to discourage misuse and abuse are also in development and/or pending at FDA, *e.g.*, Remoxy® (oxycodone controlled-release) Capsules.[69]

But for generic versions of the thirty-year-old product Talwin Nx, no generic versions of the above-referenced products have been approved. FDA has yet to issue any formal guidance generally addressing approval standards applicable to ANDAs that reference products specifically formulated to discourage abuse and misuse, although this topic may be included in the anticipated Agency guidance on abuse-deterrent drug products. Similarly, Purdue is not aware of any informal guidance provided to potential ANDA applicants on these issues. Very recently, FDA issued a guidance outlining bioequivalence testing requirements for generic versions of Embeda that recommends comparative *in vivo* bioequivalence testing of oral administration of the test and reference products following crushing for purposes of assessing morphine and naltrexone bioequivalence "in a potential abuse situation."[70] However, the Embeda guidance only addresses the bioequivalence data requirements and does not indicate what CMC or other

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[67] *See* Approval Letter for Oxecta™ (oxycodone hydrochloride) Tablets, 5 mg and 7.5 mg, available at: http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2011/202080s000ltr.pdf.

[68] Endo Pharmaceuticals Press Release, *Endo Announces FDA Approval of a New Formulation of Opana® ER Designed To Be Crush-Resistant*, available at: http://phx.corporate-ir.net/phoenix.zhtml?c=123046&p=irol-newsArticle&ID=1638555&highlight= ; *see also* Drugs@fda.gov, Entry for Opana, NDA 201655, available through a search for "Opana" at: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Overview&DrugName=OPANA%20ER.

[69] RemoxyXRT™ (oxycodone controlled-release) Capsules CII, Advisory Committee Briefing Materials for the Anesthetic Life Support Drugs Advisory Committee Meeting of November 13, 2008 (Oct. 12, 2008), available at: http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4395b1-02-PAIN.pdf.

[70] *See Draft Guidance on Morphine Sulfate; Naltrexone Hydrochloride* (June 2012), available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM308060.pdf.

requirements might need to be met for a product to be approved as a generic version of the tamper-deterrent Embeda product. In addition, while methods addressed in the new guidance might be sufficient for a product intended to deter abuse through pharmacologic properties, those methods are plainly insufficient for products utilizing physical properties to deter tampering and abuse, such as reformulated OxyContin.[71]

While FDA has not publicly announced any such policies or standards, the Agency has historically considered it inappropriate to approve a follow-on product with a higher abuse potential than the pioneer product. FDA stated this policy in the context of generic copies of products found effective through the Drug Efficacy Study Implementation ("DESI") program – a context in which the Agency had far greater flexibility to allow the marketing of follow-on products that differed from pioneer products than it now does under the Hatch-Waxman amendments. In particular, FDA determined that firms were often submitting ANDAs for products that differed from the products found effective during the DESI review. The Agency proposed and ultimately adopted changes to its regulations providing that ANDAs were appropriate for products identical to DESI drugs, and firms could petition the Agency for a determination as to the appropriateness of ANDAs for similar or related drug products that differed from the subject DESI drug. In discussing the proposed changes, FDA explained that ANDAs are appropriate for proposed products so closely related to the DESI drug that qualified experts could be expected to conclude that the available information supporting the safety and effectiveness of the DESI drug would also apply to the related drug. However, 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.[72] This historical policy, that sensibly recognizes attributes bearing on abuse as critical safety parameters, is of even greater significance now that the Agency must consider ANDAs submitted under current standards for purported generics of

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[71] This Petition addresses approval standards applicable to proposed generic versions of products that are intended to resist tampering and manipulation through unique physicochemical properties, and the requested actions pertain, in particular, to the requirements applicable to generic versions of reformulated OxyContin. ANDAs for other opioids that have been formulated to discourage abuse and/or misuse may warrant different standards. For instance, it may be necessary to require different tests and criteria for evaluating proposed generic copies of pioneer products such as Talwin Nx, Suboxone, and Embeda that seek to impede tampering and abuse through use of a non-absorbed active ingredient, or an active ingredient present at levels which would have an effect only through unintended routes of administration.

[72] *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).

reformulated OxyContin and other products designed with physicochemical properties or additional ingredients intended to impede abuse and misuse.[73]

Consistent with the longstanding policy first implemented during the DESI review, FDA's mandate to protect and promote the public health, as well as the recent White House efforts to stem the tide of prescription opioid abuse, it is essential that FDA ensure that products purporting to be generic versions of brand name products specifically formulated to discourage abuse and misuse actually duplicate the defining features of those innovative products. 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 Agency has committed to the public that generic drugs have the same risk-benefit profile and are duplicates of brand name drugs in terms of safety and performance characteristics. *See* Section II.B. above. Epidemiologic data now indicate that the unique physicochemical attributes of reformulated OxyContin impact the safe use of the product by patients who might otherwise inadvertently misuse the product as well as by would-be abusers. The epidemiologic data also indicate that Purdue's comprehensive battery of *in vitro* experiments are predictive of real world experience. Accordingly, the Agency's commitments about the safety of generic drugs require that any generic copy be shown, through comprehensive, comparative *in vitro* testing and one or more comparative *in vivo* studies of manipulated product, to perform as well as OxyContin when subjected to known and anticipated methods of tampering. Absent such data from carefully designed studies that systematically evaluate the physicochemical properties of the product when subjected to experimental conditions simulating tampering, there would be no basis to conclude that the proposed generic product had the same risk-benefit profile as OxyContin, was as safe as OxyContin, or performed the same as OxyContin.

In addition to contradicting the common and long-held understanding of what a generic drug is, approval of a generic version of OxyContin that did not duplicate the physicochemical properties of OxyContin would also have a number of other detrimental effects. As Dr. Cone explains in his Declaration:

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[73] Recently, the Agency has reaffirmed that differences between generic and pioneer products that may impact safety can preclude ANDA approval. As reported in a law firm blog, the Office of Generic Drugs recently issued letters to companies with pending ANDAs advising that their applications were not approvable due to the proposed products having larger tablet sizes than the referenced listed drugs. The letters reportedly state, "The larger tablet size poses greater potential safety issues such as choking, tablet arrest, and prolonged transit time, which could result in esophageal injury and/or pain. The larger tablet size also raises product efficacy concerns due to patients' inability or unwillingness to swallow the larger tablets. . . . Therefore, from a clinical standpoint, this product is unacceptable for approval as a generic and we recommend that you redesign your product to be closer in size to the relevant strengths of the RLD." *See* "Size Matters" Says FDA, When it Comes to Generic Drug-RLD Sameness, available at: http://www.fdalawblog.net/fda_law_blog_hyman_phelps/2012/01/size-matters-says-fda-when-it-comes-to-generic-drug-rld-sameness.html.

> . . . it is my strongly held professional opinion that FDA should not approve generic versions of reformulated OxyContin that do not perform as well as reformulated OxyContin when tested in (a) *in vitro* experiments intended to simulate attempted tampering by potential abusers or by patient/caregivers inadvertently misusing the medication, and (b) one or more comparative *in vivo* bioavailability studies of tampered product. Approval of such a product as a generic version of OxyContin would very quickly eliminate the positive public health benefits of reformulated OxyContin. In virtually all states, once FDA has approved a generic version of a brand name drug product, pharmacists are either authorized or required by law to fill prescriptions with the generic product, generally without consultation with the prescriber. While most of these state laws also allow prescribers to take affirmative steps to specify that the brand name product must be dispensed, effectively overriding mandatory substitution, many insurance carriers will not cover the cost of brand name products when a generic version is available, and thus for many patients it may not be practical to write prescriptions in this manner. Moreover, sponsors of tamper-resistant products (potentially including both Purdue and sponsors of tamper-resistant generics) that are unable to differentiate their products from non-tamper-resistant generics due to promotional limitations would be unable even to attempt to educate prescribers and pharmacists about the risks of prescribing or dispensing non-tamper-resistant products. In light of these factors, it is reasonable to expect that the result of these mandatory substitution laws would be to flood the marketplace with generic products that do not have the same resistance to manipulation and tampering as reformulated OxyContin. Based on trends in communication among drug abusers, I would expect potential abusers to very quickly learn that a readily crushable version of extended release oxycodone is once again available. I would further expect, in light of mandatory substitution and rapid experimentation with and communication about generic products by abusers, that abuse of extended release oxycodone could return to the levels experienced prior to introduction of reformulated OxyContin.

Exhibit 22, ¶ 11 (footnote omitted).

Dr. Cone's conclusions concerning the impact of market forces were echoed at the 2009 Advisory Committee hearing at which the *in vitro* data on reformulated OxyContin were considered. At the hearing, Elaine Morrato, Dr.P.H., M.P.H., C.P.H., an epidemiologist from the Colorado School of Public Health, University of Colorado, and a member of the Drug Safety and Risk Management Advisory Committee, recognized that any safety advantage offered by reformulated OxyContin would be fleeting if non-tamper

resistant generic extended release oxycodone were approved, due to market forces driving use of less expensive generics.[74]

Dr. Cone also identified a number of other consequences associated with approval of generic versions of reformulated OxyContin that had not been shown to duplicate its innovative physicochemical attributes:

> FDA approval of generic versions of reformulated OxyContin that have not been shown to perform as well as reformulated OxyContin in such *in vitro* and *in vivo* experiments would also have several other ramifications. First, the ability to monitor and measure the benefits of reformulated OxyContin through continuing epidemiological studies would be compromised, if not entirely eliminated. Second, the incentives to invest in the significant research and development necessary to bring tamper-resistant products to market would be substantially reduced. I cannot conceive of a scenario in which a public health agency such as the FDA could rationalize such a result. Indeed, I believe it would be counter to FDA's role to approve a generic version of OxyContin that had not been shown, through comprehensive *in vitro* and *in vivo* testing, to perform as well as OxyContin when subjected to known and anticipated methods of tampering.

Exhibit 22, ¶12 (footnote omitted).

Dr. Cone's concern about erosion of the public health benefits of reformulated OxyContin was recently echoed by the Minister of Health and Long-Term Care, Ontario, the Honorable Deborah Matthews. Reformulated OxyContin has been distributed by Purdue Canada, under the tradename OxyNEO, since March 1, 2012. In a letter to the Honorable Leona Aglukkaq, Minister of Health, Canada, Ms. Matthews urged that Health Canada refuse to authorize the sale of non-tamper resistant generic versions of OxyNEO.[75] In her letter, Ms. Matthews expresses her concern that the benefits associated with OxyNEO would be "eroded by the re-introduction of the non-tamper-resistant formulation to the Canadian market." She further explains:

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[74] *See* Transcript of September 24, 2009 Joint Meeting of the Anesthetic and Life Support Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee, pp. 254-56, available at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndLifeSupportDrugsAdvisoryCommittee/UCM187082.pdf.

[75] *See* Letter to the Honorable Leona Aglukkaq, Minister of Health, Canada, from the Honorable Deborah Matthews, Minister of Health and Long-Term Care, Ontario (June 6, 2012), attached hereto as Exhibit 25. We believe this letter may have been misdated and that it may have actually been sent on July 6, 2012 (not June 6). A copy was received by Purdue Pharma L.P. on July 9, 2012.

> . . . I understand generic manufacturers may have submitted their products for approval to market in Canada. To the best of our knowledge, generic oxycodone CR will not be formulated to be tamper-resistant. Moreover, given the potential for widespread abuse and the susceptibility to diversion and trafficking of this product, we believe that approving the generic oxycodone CR tablets for sale in Canada would further exacerbate the incidences of addiction and death in Canada and contribute to a growing public health crisis. . . . Ontario believes that the costs to society of the reintroduction of the more-easily abused version far outweigh the financial benefits that would accrue from the reduced price we would receive and, as you know, Ontario has the most aggressive generic pricing policy in the country. However, only the Federal Government has the authority to approve the sale of generic oxycodone in this country. For this reason I am seeking your help and am strongly urging you not to grant market authorization for generic versions of oxycodone CR tablets in Canada.

Exhibit 25, p. 2. We are not aware that Health Canada has made a decision on this issue.

In sum, requiring that ANDAs citing reformulated OxyContin as the reference listed drug include the type of comparative *in vitro* and *in vivo* data discussed herein furthers ongoing efforts to reduce abuse of prescription drugs and is fully consistent with longstanding Agency policy, as well as the policy reflected in FDA's recent bioequivalence guidance on generic versions of Embeda. On the other hand, permitting the marketing of a "generic" version of reformulated OxyContin that has not been shown to perform as well as reformulated OxyContin under conditions designed to simulate tampering would have a number of detrimental effects and would be flatly inconsistent with the Agency's mission to promote and protect the public health.

2. Generic Versions of OxyContin Must be Evaluated in a Comprehensive Battery of *In Vitro* Tests Designed to Simulate Tampering and in One or More *In Vivo* Studies of Manipulated Product

As explained above, and in more detail in the accompanying Declaration of Edward J. Cone, Ph.D., extended release oxycodone products which seek approval through ANDA submissions listing reformulated OxyContin as the reference listed drug must be evaluated in a comprehensive battery of *in vitro* tests designed to simulate common methods of tampering and in one or more comparative *in vivo* bioavailability studies of manipulated product. In order to provide valid, relevant data, such *in vitro* evaluation should adhere to the criteria set by the FDA and the Advisory Committee for the evaluation of reformulated OxyContin (*see* Section II.A.3. above). In addition, the development of *in vitro* and *in vivo* test methodology should follow the iterative approach

of adapting the specific tests to what is known (and discovered during testing) about each formulation. As Dr. Cone states in his declaration:

> Test methods employed by generic applicants should be the same as those developed and validated by Purdue, using reformulated OxyContin as a control. Alternatively, new methods could be developed based on input from external experts experienced in drug abuse treatment and tampering methods, and knowledgeable about extraction techniques suitable for purification of oxycodone from complex matrices and excipients. Any new methods developed must comprehensively identify and characterize the physicochemical attributes of the generic formulation in comparison to reformulated OxyContin, and also adhere to the general principles stated above in order to yield reliable scientific data (*see* Paragraphs 14-15 above).
>
> In addition, generic manufacturers must also carefully consider the specific physical and chemical features of the proposed generic product, and any physicochemical differences between reformulated OxyContin and the proposed generic product. Any potential formulation-specific vulnerabilities associated with physical and chemical features of the generic product must also be explored through comprehensive *in vitro* testing, using reformulated OxyContin as a control.
>
> As a general matter, the results of all of these *in vitro* tests should be the subject of 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. Thus, for instance, for each test parameter, the difference between the proposed generic product's test data and comparable tests of reformulated OxyContin, given a robustly powered experiment, should not be significantly different at a 95% confidence level.
>
> Proposed generic products should also be evaluated in one or more *in vivo* bioavailability studies designed to compare release of oxycodone from tampered product and tampered reformulated OxyContin. Initial testing should entail a comparison of the bioavailability of finely crushed generic product with finely crushed reformulated OxyContin following oral administration (*e.g.*, equivalent particle size bands as discussed in ¶¶ 18-21 above). Results of this initial *in vivo* test as well as the results of the *in vitro* experiments discussed herein, and the specific physical and chemical attributes of the proposed generic product, should then be considered to determine whether additional *in vivo* testing of different tampered states (*e.g.*, coarsely crushed) and/or different routes of administration (*e.g.*,

> intranasal) are necessary to adequately assess whether the proposed generic product can be expected to perform as well as reformulated OxyContin when subjected to known and anticipated forms of tampering. As discussed above regarding *in vitro* tests, the results of all *in vivo* tests should be the subject of statistical analyses which support the conclusion that the rate and extent of release of oxycodone from the proposed generic product is no greater than the rate and extent of release from reformulated OxyContin. Such *in vivo* studies would provide necessary confirmation that the comprehensive battery of *in vitro* experiments adequately demonstrates that the tamper resistant features of the products are comparable.

Exhibit 22, ¶¶ 23-26 (footnote omitted). Dr. Cone's Declaration provides further specific detail concerning the manner in which these tests should be designed so as to generate reliable data characterizing the physicochemical attributes of the proposed generic product when subjected to known and anticipated methods of tampering. *See* Exhibit 22, ¶¶ 14-22.

In order to assure that all potential generic applicants are apprised of the tests to be performed, FDA should adopt and announce a guidance addressing the *in vitro* and *in vivo* tests that must be performed to characterize the physicochemical properties of the proposed generic product and to assess the rate and extent to which oxycodone is released when the product is subjected to manipulations designed to simulate attempts to tamper with the product for purposes of abuse or misuse. While Purdue believes general requirements are best announced publicly in a guidance document, the company shares FDA's historical concern that information on *in vitro* test methodology released publicly not be so specific as to aid would-be abusers in devising potential ways to extract oxycodone from reformulated OxyContin or any future generic product. Accordingly, Purdue 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 ANDA applicants.

Should the Agency conclude that it would benefit from further expert input addressing the nature of the *in vitro* and *in vivo* studies that should be performed on proposed generic copies of OxyContin, beyond that provided in the Declaration of Dr. Cone, the Agency could convene a joint meeting of Anesthetic and Analgesic Drug Products and Drug Safety and Risk Management Advisory Committees.

3. FDA Has Ample Legal Authority to Require *In Vitro* Tamper Testing and *In Vivo* Testing of Manipulated Product, and Refuse to Approve Proposed Generic Products that Do Not Satisfy the Acceptance Criteria

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.[76] With the submission of ANDAs citing reformulated OxyContin as the RLD and additional ANDAs citing Embeda and Opana ER as the RLD,[77] the Agency must consider how to address the important advances in pharmaceutical science represented by these and other products designed to impede abuse and misuse. 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 as, 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 versions of OxyContin 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.[78] FDA may require that applicants seeking to market generic versions of OxyContin perform such *in vitro* tamper testing and *in vivo* testing of manipulated product under four different sets of statutory and regulatory provisions, each of which is discussed below.

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[76] *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.

[77] Embeda and Opana ER appear on the FDA-maintained list of list of drug products for which an ANDA has been received by the Office of Generic Drugs containing a Paragraph IV patent certification. *See* List, available at: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM293268.pdf.

[78] 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, 2012 U.S. Dist. LEXIS 14873, at * 18-43, Civil Action No. 10-01255 (ABJ) (D.D.C. Feb. 7, 2012).

(a) 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). To appropriately acknowledge the public health significance of increasingly specialized dosage forms designed to impede manipulation, tampering, abuse, or misuse, the Agency must recognize that such a dosage form which has been specifically designed and demonstrated to be more difficult to prepare for abuse/misuse via one or more routes of administration, whatever dosage form it might superficially resemble, is not the same as a non-tamper-resistant, conventional, dosage form. In the case of OxyContin, a proposed generic product that is not shown, through comprehensive *in vitro* testing and one or more comparative bioavailability studies of manipulated product, to perform as well as OxyContin when subjected to known and anticipated methods of tampering, is not the same dosage form as reformulated OxyContin and is therefore not approvable. [79]

(1) General Agency Approach To Distinguishing Among Dosage Forms

Classifying reformulated OxyContin as a different dosage form from a conventional "tablet," is consistent with applicable regulations and policies, as well as past Agency decisions. The only FDA regulation that further defines the statutory requirement that ANDAs contain information showing that the proposed "dosage form" is the "same as" the RLD states that the phrase "same as" means "identical." 21 C.F.R. § 314.92(a)(1). Neither the FDCA nor FDA's implementing regulations further define or address different dosage forms. No provision identifies additional factors which will be

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[79] To our knowledge, FDA has not previously distinguished between conventional dosage forms and dosage forms designed with physicochemical attributes specifically intended to impede manipulation and tampering for purpose of determining whether a generic product is the same dosage form as the pioneer under 21 U.S.C. § 355(j)(4)(D) and 21 C.F.R. § 314.127(a)(4). Generic versions of the few pioneer products that fall into this unique and evolving category have not yet been approved and it appears the Agency has not had the occasion to determine whether products specifically designed to resist manipulation for purposes of abuse or misuse are novel dosage forms. Though the Agency has not previously distinguished among dosage forms on this basis, it is appropriate and necessary that it acknowledge this new and expanding category of specialized drug products in its dosage form classifications. "Flexibility and adaptability" are "an essential part of the office of a regulatory agency." *American Trucking Ass'n v. Atchison, Topeka and Santa Fe Ry. Co.* 387 U.S. 397, 416 (1967) (agencies are "neither required nor supposed to regulate the present and the future within the inflexible limits of yesterday"); *see also Detsel v. Sullivan*, 895 F.2d 58, 64 (observing that "agencies must interpret their regulations in light of changing circumstances, particularly in areas characterized by rapid technological development" and rejecting as unreasonable agency interpretation of regulations based on "static and obsolete" medical assumptions).

considered in determining whether two dosage forms are the same or not for purposes of ANDA approval.

Appendix C of the Orange Book lists a number of different dosage forms, each of which is treated as different for purposes of 21 U.S.C. § 355(j)(4)(D) and 21 C.F.R. § 314.127(a)(4), including nine types of tablet dosage forms.[80] The list at Appendix C is not binding on FDA or upon industry, however, and instead merely serves as informal guidance to industry on what categories of dosage forms FDA has thus far chosen to identify.[81] Appendix C does not include or reference any definitions of these identified dosage forms, but none of the currently identified tablet types adequately capture the unique attributes of reformulated OxyContin that distinguish the product from conventional tablets.[82] Historically, when FDA concludes that another dosage form should be recognized for purposes of Orange Book listings and product approvals, FDA adds that dosage form to the list provided at Appendix C.[83] Consistent with this practice, FDA should either characterize OxyContin as a different type of tablet dosage form, such as "modified tablet" and add this dosage form to Appendix C, or otherwise acknowledge that tamper resistance is an additional, critical factor in assessing dosage form "sameness" for OxyContin and other similarly situated products.

Neither the statute nor FDA regulations identify the factors which will be considered in determining whether two dosage forms are the same for purposes of ANDA approval. Neither has FDA articulated a universally-applicable standard. FDA has, however, resolved a number of product-specific disputes concerning this issue. From

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80 The nine types of tablets currently listed in the Orange Book are: tablet; tablet, chewable; tablet, coated particles; tablet, delayed release; tablet, delayed release, orally disintegrating; tablet, effervescent; tablet, extended release; tablet, for suspension; and tablet, orally disintegrating. *Approved Drug Products with Therapeutic Equivalence Evaluations* ("Orange Book"), 32nd Ed. (2012), at Appendix C, available at: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/UCM071436.pdf.

81 *Pfizer, Inc. v. Shalala,* 1 F.Supp.2d 38, 45-46 (D.D.C. 1998), *aff'd in part, rev'd in part, Pfizer, Inc. v. Shalala,* 182 F.3d 975 (D.C. Cir. 1999); *see also* Response to Citizen Petitions, Docket Nos. 2004P-0506, 2004P-0472, 2004P-0540, and 2004P-0340 (Jan. 28, 2005), at p. 3, available at: http://www.fda.gov/ohrms/dockets/dockets/04p0472/04p-0472-pdn0001.pdf.

82 CDER's Data Standards Manual includes definitions for multiple dosage forms, including nineteen separate types of tablets. These various definitions also fail to capture the unique attributes of OxyContin. *See CDER Data Standards Manual, Drug Nomenclature Monographs, Dosage Form, C-DRG-00201,* Version 008, available at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/DataStandardsManualmonographs/ucm071666.htm.

83 *See* Response to Citizen Petitions and Petitions for Stay of Action, Docket No. 96P-0459 (Nov. 2, 1998), at p. 6, attached hereto as Exhibit 23 (describing additions to Appendix C to recognize "solution, microemulsion" and "capsule, microemulsion").

these Agency decisions, it appears that two factors to consider are the physical appearance of the drug products and the way the drug products can be administered. The agency has also indicated that a dosage form should not be so narrowly defined as to be product-specific.

a. Physical Appearance and Manner of Administration

FDA's determination that tablets and capsules are different dosage forms illustrates the manner in which physical appearance and the way drug products can be administered are factored in to dosage form distinctions for ANDA approval purposes.[84] In rejecting two Citizen Petitions that had requested that FDA treat tablets and capsules as the same dosage form, FDA explained that it has historically distinguished dosage forms on the basis of the physical appearance of the drug and the way it is administered.[85] The Agency concluded that there were important physical differences between tablets and capsules that warranted continued treatment as different dosage forms. For example, tablets, particularly those that are scored, can be divided to provide a smaller dose, including doses suitable for titration. In contrast, some capsules can be opened and sprinkled on food to facilitate ingestion. In addition, many individual patients find either capsules or tablets easier to swallow. Ultimately, FDA concluded that while tablets and capsules are similar in many respects, they each "have special properties that may make one or the other more advantageous in the treatment of certain patients. Tablets and capsules, therefore, should not be regarded as the same dosage form."[86]

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[84] Response to Citizen Petitions, Docket Nos. 95P-0262 and 96P-0317 (Dec. 1, 2000), available at: http://www.fda.gov/ohrms/dockets/dailys/00/Dec00/120700/pdn001.pdf. *See also Warner-Lambert Company v. Shalala,* 202 F.3d 326 (D.C. Cir. 2000) (affirming District Court denial of injunction against FDA, finding FDA had applied physical appearance and manner of administration criteria to conclude a generic tablet inside a capsule is the same dosage form as Dilantin capsules).

[85] Response to Citizen Petitions, Docket Nos. 95P-0262 and 96P-0317 (Dec. 1, 2000), at p. 4, available at: http://www.fda.gov/ohrms/dockets/dailys/00/Dec00/120700/pdn001.pdf.

[86] While the Agency typically refers to the way a product is administered when listing the criteria for distinguishing between dosage forms, the examples provided by FDA in response to the tablet/capsule petitions (cut tablets, sprinkled capsules) illustrate that the critical issue is the way a product *can be* administered. Similarly, the Agency has stated that this criterion encompasses more than the simple mode of administration. *Warner-Lambert Co. v. Shalala,*202 F.3d 326, 329 n.3 (D.C. Cir. 2000) ("The scope of the 'administration' part of the dosage form definition remains unclear. FDA acknowledges that the 'method of administration' is more subtle than simply distinguishing between the manner in which the drug is introduced to the patient, such as orally, topically, or via injection. But we have no occasion to probe the contours of 'method of administration' in this case because there is no allegation that Dilantin and Mylan's product have different methods of administration").

b. Preference for Non-Product-Specific Dosage Forms

The preference that dosage form classifications not be product-specific is illustrated in a case upholding FDA's refusal to acknowledge dosage form distinctions based on differences in drug release mechanism.[87] The Agency had denied a Citizen Petition advocating that FDA divide the extended-release tablet dosage form into seven separate dosage forms distinguished by the mechanism through which the extended-release tablet delivers the active ingredient.[88] FDA reasoned that the proposed classification system, in which many dosage forms would be product-specific, would impede generic substitution and improperly suggest differences between products that do not correspond to clinical distinctions.[89] The United States District Court for the District of Columbia rejected a challenge to FDA's refusal to alter its classification system.[90]

(2) Dosage Forms Which Have Demonstrated Tamper-Resistant Features Should be Recognized As Different

Products designed, and shown through comprehensive *in vitro* testing, to resist known and expected real-world methods of manipulation for purposes of abuse or misuse cannot rationally be considered the "same as" conventional dosage forms, much less "identical" to them, as is required by FDA regulations at 21 C.F.R. § 314.92(a)(1). Such products are fundamentally different from superficially similar-looking conventional products in terms of their safety, abuse potential, and substitutability – as has now been additionally confirmed through epidemiologic studies of the impact of the OxyContin

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87 *Pfizer, Inc. v. Shalala,* 1 F.Supp.2d 38, 45-46 (D.D.C. 1998), *aff'd in part, rev'd in part, Pfizer, Inc. v. Shalala,* 182 F.3d 975 (D.C. Cir. 1999). Other Citizen Petition decisions also reflect the Agency position that dosage forms should not be drawn so narrowly as to be product specific. *See* Response to Citizen Petitions and Petitions for Stay of Action, Docket No. 96P-0459 (Nov. 2, 1998), at p. 14, attached hereto as Exhibit 23.

88 Response to Citizen Petition and Petition for Stay of Action, Docket No. 93P-0421 (Aug. 12, 1997), at p. 6, attached hereto as Exhibit 24.

89 *Id.* at 7.

90 *Pfizer, Inc. v. Shalala,* 1 F.Supp.2d 38, 45-46 (D.D.C. 1998), *aff'd in part, rev'd in part, Pfizer, Inc. v. Shalala,* 182 F.3d 975 (D.C. Cir. 1999). FDA concluded that required bioequivalence studies would identify any differences in the rate of absorption between extended-release products with different release mechanisms. Response to Citizen Petition and Petition for Stay of Action, Docket No. 93P-0421 (Aug. 12, 1997), at pp. 11-14, attached hereto as Exhibit 24. In the case of reformulated OxyContin, in contrast, typical fed and fasted single-dose bioequivalency studies would not identify any differences in the products' performance when subjected to known and anticipated methods of tablet manipulation or tampering.

reformulation. Moreover, the difference between conventional dosage forms and such alternate dosage forms is much more significant in a practical sense than dosage form distinctions that are currently recognized, such as tablet vs. capsule, lotion vs. cream, "lotion/shampoo" vs. shampoo, "cream, augmented" vs. "lotion, augmented."[91]

Further, identifying reformulated OxyContin as a novel dosage form such as "modified tablet," or simply acknowledging that it is not an ordinary tablet, is consistent with FDA's historical focus on the appearance of a product and the way it may be administered. Conventional tablets such as original OxyContin are readily subject to tampering and may be taken via multiple routes of administration. In contrast, Purdue's *in vitro*, *in vivo,* and epidemiologic data show that reformulated OxyContin is more difficult to prepare for misuse or abuse via multiple routes of administration. Specifically, reformulated OxyContin is difficult to break or crush and is only deformed by most manual methods. The inability to readily crush reformulated OxyContin is a significant impediment to many forms of abuse as well as misuse by patients or their caregivers, *e.g.,* crushing for administration via gastric tube. In addition, the formulation forms a viscous hydrogel when hydrated, even in small volumes of water, which is a significant impediment to intranasal and intravenous abuse. In sum, these unique physicochemical attributes significantly impact the manner in which reformulated OxyContin can be administered to patients and to non-patient, would-be-abusers. In addition, while reformulated OxyContin has the appearance of a conventional tablet when taken as directed, if instead the product is subject to tampering it no longer appears the same as a conventional tablet, *e.g.,* deformed or broken into large pieces rather than powdered, a gelatinous mass rather than an injectable solution. Importantly, classification of reformulated OxyContin as a "modified tablet," or using similarly descriptive terms, effectively distinguishes this novel dosage form from its conventional counterpart without being product-specific. Such a descriptive term is, instead, broad enough to encompass any number of different technologies, mechanisms, or ingredients that may be used to impart attributes similar to those of reformulated OxyContin.[92]

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[91] *Approved Drug Products with Therapeutic Equivalence Evaluations* ("Orange Book"), 32nd Ed. (2012), at Appendix C, available at: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/UCM071436.pdf.

[92] FDA has previously used the term "modified" to distinguish between two bioinequivalent cyclosporine formulations that were determined not to warrant treatment as different dosage forms. *See* Response to Citizen Petitions and Petitions for Stay of Action, Docket No. 96P-0459 (Nov. 2, 1998), at pp. 17-18, attached hereto as Exhibit 23. Use of "modified" in that context does not preclude classification of reformulated OxyContin as a "modified tablet" dosage form. Alternatively, another broad term could be used to distinguish reformulated OxyContin from conventional tablet dosage forms. By way of example, in the future, should the OxyContin labeling be modified accordingly to reflect these product characteristics, it may be appropriate to describe the dosage form differently, *e.g.,* "tamper resistant tablet" or "abuse deterrent tablet." In any event, the semantics of how the critical uniqueness of the dosage form is described are unimportant, as long as the Agency properly indicates that reformulated OxyContin is not the same dosage form as an extended release tablet that can be readily abused or

To the best of our knowledge, FDA has considered possible dosage form distinctions based on potential differences in abuse liability in only one situation. In a 2004 Citizen Petition, Alza, the manufacturer of Duragesic®, requested that FDA classify matrix and reservoir fentanyl transdermal systems, as well as products with and without rate-controlling membranes, as different dosage forms that are not pharmaceutical equivalents. At the time, Duragesic was a reservoir transdermal system utilizing a rate-controlling membrane to regulate the rate of drug delivery,[93] while certain pending ANDAs sought approval of matrix systems, at least one of which did not employ a rate-controlling membrane. Alza argued that only those generic products using both a reservoir system and a rate-controlling membrane should be considered the same dosage form as Duragesic. According to Alza, differences in potential abuse liability and drug delivery warranted classifying each type of system as a different dosage form. With respect to abuse liability, Alza theorized that (1) the ability to cut matrix patches into small segments would facilitate their use as party drugs, (2) fentanyl may be more rapidly and completely extracted from a matrix system than from a reservoir system, based on an experiment in which Duragesic and Alza's European matrix system patch were soaked at room temperature in various solvents, and (3) matrix systems were rated more attractive to potential abusers than Duragesic, based on product descriptions. Generic applicants vigorously disputed Alza's conclusions concerning ease of abuse of matrix systems and further argued that the Duragesic reservoir system presented a greater risk of abuse because the concentrated dose of fentanyl contained in the reservoir could be readily obtained, *e.g.*, by cutting open the reservoir or extracting the contents with a syringe. Significantly, no company claimed to have designed its transdermal system to resist any form of tampering, or to have tested its system to characterize the performance of the product when exposed to known and anticipated forms of tampering or manipulation. Indeed, Alza argued that the Duragesic reservoir system was not subject to significant abuse, and matrix system products had not yet been approved in the United States, so there was no experience with abuse of that type of system.

FDA denied Alza's petition, concluding that the various types of fentanyl transdermal systems would be classified as the same dosage form, "film, extended-release." The Agency determined that the transdermal systems differed in release mechanism rather than dosage form. With respect to abuse liability, FDA concluded that both matrix and reservoir systems could be abused and that Alza had not shown that

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misused through crushing or dissolving and that, therefore, *in vitro* tests are necessary to establish whether a proposed generic product qualifies as the same dosage form.

[93] Subsequently, in July 2009 FDA approved a supplement for Duragesic to change its formulation from a reservoir patch to a matrix patch. *See* Response to Petition for Stay of Action, Docket FDA-2009-P-0415 (Feb. 22, 2010), at p. 2, available at: http://www.regulations.gov/#!documentDetail;D=FDA-2009-P-0415-0007.

matrix systems have a greater abuse liability potential than reservoir ones. The Agency declined to distinguish the products in terms of dosage form based on "theoretical differences in potential abuse liability."[94]

Reformulated OxyContin, on the other hand, presents entirely different considerations which dictate a different conclusion. Unlike matrix systems that had never been marketed, controlled-release oxycodone in conventional tablet dosage form was marketed for many years by Purdue and, for a time, by generic companies, and there is a great deal of experience with abuse and misuse of these products. Abuse and misuse persisted despite implementation of a number of initiatives designed to help curb abuse and misuse. In response to reports of abuse of original OxyContin, Purdue embarked on a targeted development program with the goal of designing a tamper-resistant oxycodone product that was bioequivalent to the original formulation of OxyContin. The resulting product, reformulated OxyContin, was required by FDA to be comprehensively tested to characterize its unique physicochemical attributes when subjected to techniques intended to simulate known and anticipated methods of tampering – even though no labeling claims of tamper resistance were proposed to be made. These *in vitro* data identify a number of differences in the way reformulated and original OxyContin may be administered, as well as differences in appearance when subject to attempted tampering. Published data from epidemiologic studies of the impact of the reformulation indicate that reformulated OxyContin is *in fact* administered differently from original OxyContin by patients entering substance abuse treatment centers in the NAVIPPRO system and by a cohort of individuals in eastern Kentucky who had abused the original formulation of OxyContin prior to the introduction of reformulated OxyContin. Both studies show reductions in rates of abuse through non-oral administration – the specific routes targeted by the reformulation. In addition, published epidemiologic data also show reductions in rates and frequency of OxyContin abuse, reductions in drug diversion activity involving OxyContin, and reductions in intentional and unintentional poisonings and adverse events involving OxyContin. Thus, unlike the situation presented by the Alza petition, there are not mere "theoretical differences in potential abuse liability" but, instead, documented differences that enhance the safe use of extended-release oxycodone by patients as well as would-be abusers.

In sum, in the case of OxyContin, the novel physicochemical attributes are therapeutically significant and critical to the performance of the product. Consistent with the Agency's historical approach to distinguishing among dosage forms, reformulated OxyContin should therefore be classified as a distinct dosage form, separate from

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[94] Response to Citizen Petitions, Docket Nos. 2004P-0506, 2004P-0472, 2004P-0540, and 2004P-0340 (Jan. 28, 2005), at pp. 3-5, 6-7, available at: http://www.fda.gov/ohrms/dockets/dockets/04p0472/04p-0472-pdn0001.pdf.

conventional tablet dosage forms that do not share these attributes, unless the distinction is effectively addressed on another basis.[95]

(b) Bioequivalence

An ANDA must contain 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); 21 C.F.R. § 314.94(a)(7). Absent such data, the ANDA is not approvable. 21 U.S.C. § 355(j)(4)(F) ; 21 C.F.R. § 314.127(a)(6).

A proposed generic product is considered bioequivalent to the RLD if "the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses." 21 U.S.C. § 355(j)(8)(B); *see* 21 C.F.R. § 320.1(e). FDA regulations provide that "FDA may require in vivo or in vitro testing, or both, to measure the bioavailability of a drug product or establish bioequivalence. . . . The selection of the method used to meet an in vivo or in vitro testing requirement depends upon the purpose of the study, the analytical methods available, and the nature of the drug product." 21 C.F.R. § 320.24(a). FDA regulations list, in general terms, several methods that may be used to establish bioavailability or bioequivalence, including, "[a]ny other approach

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[95] The FDCA authorizes submission of a suitability petition seeking FDA permission to submit an ANDA for a dosage form that differs from the RLD. 21 U.S.C. § 355(j)(2)(C). FDA will deny such a suitability petition if the Agency determines that (a) investigations must be conducted to show the safety and effectiveness of the generic drug product, (b) the proposed change from the RLD would jeopardize the safe and effective use of the product so as to necessitate significant labeling changes to address the newly introduced safety or effectiveness problem, or (c) the RLD has been withdrawn from sale for safety or effectiveness reasons. 21 C.F.R. § 314.93(e)(1)(i), (iv), (v). Each of these grounds would necessitate denial of a suitability petition seeking permission to submit an ANDA for a version of OxyContin that does not have properties similar to those of OxyContin which render the product less susceptible to manipulation. First, investigations would be required to show the safety of a generic extended release oxycodone in a dosage form that did not impede common forms of manipulation. In particular, animal or clinical studies would be needed to establish that the risk-benefit ratio of such a product is the same as that of OxyContin. Second, as discussed in further detail in Section II.C.3.(c), a generic product in a dosage form that has not been shown to have properties similar to those of OxyContin would require significant labeling changes to alert prescribers to the differences from OxyContin. Third, a suitability petition seeking permission to file an ANDA for a dosage form not shown to impede common forms of tampering would amount to a citation to the original, now discontinued, formulation of OxyContin as the RLD. As established in Purdue's comments on three pending Citizen Petitions, the original formulation of OxyContin in a standard extended release tablet dosage form has been withdrawn from sale for safety reasons. *See* Comments of Purdue Pharma L.P. on pending petitions docketed as FDA-2010-P-0526 and FDA-2010-P-0540, and FDA-2011-P-0473, available at: http://www.regulations.gov/#!docketDetail;D=FDA-2010-P-0526;dct=FR%252BPR%252BN%252BO%252BSR and http://www.regulations.gov/#!docketDetail;D=FDA-2010-P-0540;dct=FR%252BPR%252BN%252BO%252BSR and http://www.regulations.gov/#!searchResults;rpp=25;po=0;s=fda-2011-p-0473.

deemed adequate by FDA to measure bioavailability or establish bioequivalence." 21 C.F.R. § 320.24(b)(6). Accordingly, FDA has broad discretion to insist upon bioequivalence testing appropriate to the complexities of the drug products involved. *See Schering Corp. v. FDA,* 51 F.3d 390, 399 (3d Cir. 1995) (rejecting challenge to FDA's bioequivalence regulations and noting "[a]lthough the Act mandated a showing of bioequivalence for approval, there is no evidence that Congress intended to limit the discretion of the FDA in determining when drugs were bioequivalent for purposes of ANDA approval"). FDA's general practice has been to advise potential ANDA sponsors of bioequivalence requirements through bioequivalence guidances for specific drug products.[96]

To adequately evaluate whether a proposed generic product is bioequivalent to reformulated OxyContin, it is necessary to compare performance of the products in *in vitro* experiments designed to simulate attempts at abuse and misuse and one or more comparative *in vivo* bioavailability studies of manipulated product, in addition to currently recommended single dose fed and fasted *in vivo* bioequivalence studies.[97] While bioequivalence testing for an ANDA is generally conducted under conditions consistent with the *Dosage and Administration* directions in the product labeling of the RLD, no provision in the statute or FDA's implementing regulations so limits FDA's authority and the Agency may require bioequivalence testing under additional experimental conditions.

The Agency recently exercised this broad authority, publishing guidance recommending that bioequivalence testing of generic versions of Embeda include comparative *in vivo* bioequivalence testing of crushed product to assess release and absorption of morphine and naltrexone in abuse situations.[98] Under circumstances where traditional bioequivalency testing would not evaluate important safety-related attributes, such as those presented by Embeda and other products specifically formulated to deter

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[96] *Guidance for Industry, Bioequivalence Guidance for Specific Products,* Center for Drug Evaluation and Research, Office of Generic Drugs, June 2010, available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072872.pdf.

[97] *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. To the extent that the Agency determines that the *in vitro* and/or *in vivo* experiments discussed in this Petition are considered bioequivalence requirements, this draft guidance should be modified to reflect those studies.

[98] *See Draft Guidance on Morphine Sulfate; Naltrexone Hydrochloride* (June 2012), available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM308060.pdf.

abuse or misuse, it is entirely consistent with the Agency's broad discretion to insist upon bioequivalence testing appropriate to the complexities of the drug products involved.[99]

In the case of reformulated OxyContin, it is necessary and appropriate that bioequivalence testing be conducted under conditions simulating attempted tampering that precedes inadvertent misuse by patients as well as many forms of intentional abuse. In particular, based on experience with long acting opioid drug products, the original formulation of OxyContin, generic versions of that original formulation, as well as with reformulated OxyContin, the Agency knows that would-be abusers will attempt to manipulate any controlled release oxycodone drug product. In addition, both Agency and Purdue adverse event data include documented instances of inadvertent misuse, *i.e.,* tampering to facilitate administration to patients. Thus, attempted tampering and abuse are anticipated conditions of use of any generic version of OxyContin, and bioavailability under these conditions must be assessed in order for the Agency to reach a scientifically defensible finding of bioequivalence.[100]

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[99] Courts have routinely recognized the high degree of discretion afforded the Agency in determining the methods to be used to assess bioequivalence of a proposed generic product. In rejecting a challenge to the Agency's bioequivalence regulations, the Court of Appeals for the Third Circuit observed, "[a]lthough the Act mandated a showing of bioequivalence for approval, there is no evidence that Congress intended to limit the discretion of the FDA in determining when drugs were bioequivalent for purposes of ANDA approval." *Schering Corp. v. FDA,* 51 F.3d 390, 399 (3d Cir. 1995). Other courts have reached the same conclusion. *See, e.g., Graceway Pharms. v. Sebelius,* 783 F. Supp. 2d 104, 111-12 (D.D.C. 2011) (rejecting challenge to bioequivalence requirements for topical product, noting the high degree of deference afforded to Agency determinations as to the methodologies needed to test the bioequivalency of a proposed generic product); *Astellas Pharma US, Inc. v. FDA,* 642 F. Supp. 2d 10, 19-20 (D.D.C. 2009) (rejecting challenge to bioequivalence requirements for generic drugs, noting that applicable regulations "expressly permit the FDA to employ 'any . . . approach deemed adequate by [it] to measure bioavailability or establish bioequivalence.' 21 C.F.R. § 320.24(b)"); *Bristol-Myers Squibb Co. v. Shalala,* 923 F.Supp. 212, 217-18 (D.D.C. 1996) (rejecting challenge to bioequivalence requirements imposed on generic applicant and emphasizing broad agency discretion in determining how the statutory bioequivalence requirement is to be met); *Schering Corp. v. Sullivan,* 782 F.Supp. 645, 648-51 (D.D.C. 1992) (dismissing challenge to FDA's bioequivalence requirements for nonsystemically absorbed drugs and emphasizing the Agency's broad discretion to specify the information required to show bioequivalence), *vacated as moot sub nom, Schering Corp. v. Shalala,* 995 F.2d 1103 (D.C. Cir. 1993); *Somerset Pharms. Inc. v. Shalala,* 973 F.Supp. 443, 452-54 (D. Del. 1997) (rejecting challenge to FDA's acceptance of metabolite data to show bioequivalence).

[100] Consistent with current Agency regulations and guidance, all such tests conducted on the formulation for which approval is sought must be submitted to the FDA. *Guidance for Industry, Submission of Summary Bioequivalence Data for ANDAs*, CDER, May 2011, available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM134846.pdf.

(c) Same Labeling

An ANDA must include information sufficient to show that the labeling proposed for the generic drug is the same as the labeling approved for the RLD except for changes required because of differences approved under a suitability petition or because the new drug and the listed drug are produced or distributed by different manufacturers. 21 U.S.C. § 505(j)(2)(A)(v). An ANDA that does not include such information is not approvable. 21 U.S.C. § 355(j)(4)(G); 21 C.F.R. § 314.127(a)(4).

Permissible differences in labeling are few, and notably do not include labeling intended to address safety concerns not applicable to the RLD. 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 not satisfy the labeling requirements of sections 505(j)(2)(A)(v) and [505(j)(4)(G)].[101]

A generic product that had not been shown to perform as well as reformulated OxyContin when subjected to *in vitro* and *in vivo* experiments designed to simulate

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[101] *Abbreviated New Drug Application Regulations; Proposed Rule,* 54 Fed. Reg. 28872, 28884 (July 10, 1989) (emphasis supplied). 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.

attempts to abuse or misuse the product would not be as safe for patients or would-be abusers as the RLD reformulated OxyContin. Accordingly, such a product would require significant additional safety related labeling to alert healthcare practitioners to these differences. In particular, a generic product that did not have the same safety-related physicochemical properties as reformulated OxyContin, particularly if represented to be substitutable for that formulation, would need to explicitly 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 similarly. Depending on the attributes of the generic product, it may also 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 other products.

As Dr. Cone explains in his 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 22, ¶ 12, note 5.

Moreover, to ensure key differences between OxyContin and such a generic product were understood by relevant healthcare practitioners and patients, and any 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, with 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. Yet, the statute does not permit differences among brand and generic REMS (21 U.S.C. § 355-1(i)), providing yet another reason for FDA to refuse to approve such a product.

The need for extensive disclosure of the differences in both labeling and REMS educational materials is particularly acute in light of the following: (1) repeated statements by FDA and other federal government agencies assuring healthcare practitioners and consumers that generic products are subject to the same rigorous standards and have the same risk/benefit profile of the brand name products they copy,

(2) FDA statements describing the properties of reformulated OxyContin, and (3) data from Purdue's extensive epidemiologic study program providing evidence that the reformulation has reduced: the rate and frequency of OxyContin abuse, abuse through non-oral routes (*i.e.* injecting, snorting, and smoking), drug diversion activity involving OxyContin, intentional poisonings and adverse events involving OxyContin, and unintentional poisonings and adverse events involving OxyContin, including therapeutic errors (*see* Sections II.A.5. above). As FDA has explained in the context of the "same labeling" requirement:

> Except for labeling differences due to exclusivity or a patent and differences under section 505(j)(2)(v) of the act, the ANDA product's labeling must be the same as the listed drug product's labeling because the listed drug product is the basis for ANDA approval. Consistent labeling will assure physicians, health professionals, and consumers that a generic drug is as safe and effective as its brand-name counterpart.[102]

In the context of a hypothetical generic product that is not subjected to *in vitro* and *in vivo* testing of the type described in this Petition, there would be no basis to conclude that the generic product is as safe as OxyContin. In the case of a hypothetical generic product that is tested, but fails to meet the specified acceptance criteria, available evidence would indicate that the generic product is not as safe as OxyContin. In either situation, clear label warnings would be required, precluding a finding that the labeling of the generic is the "same" as that of OxyContin.

(d) 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 submitted in the application or any other information available to the Secretary 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). FDA may refuse to approve an ANDA on these grounds when there is a reasonable basis to conclude that one of the inactive ingredients or the composition of

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[102] *Abbreviated New Drug Application Regulations; Final Rule,* 57 Fed. Reg. 17950, 17961 (April 28, 1992).

the generic drug raises serious questions about the drug's safety; the act does not require proof that the product is unsafe.[103]

These provisions authorize FDA to require *in vitro* and *in vivo* testing described in Section II.C.2. above in order to characterize the inactive ingredients in and composition of proposed generic versions of reformulated OxyContin. As the Agency itself noted in a recent Citizen Petition response, FDA has significant discretion to determine what information is required to assess the safety of inactive ingredients:

> As with all of the Agency's technical and scientific conclusions concerning the safety and efficacy of drugs and drug ingredients, the Agency's judgments concerning what the applicant must do to satisfy its burden [to establish the safety of inactive ingredients], what constitutes a "serious question of safety," and what information it can or should rely on to reach these judgments are matters that "fall squarely within the ambit of the FDA's expertise and merit deference" from the courts (*Schering Corp. v. FDA,* 51 F.3d 390, 399 (3rd Cir. 1995)).[104]

Given the unique attributes imparted by the inactive ingredients in reformulated OxyContin, it is necessary and appropriate for the Agency to require a generic applicant to conduct *in vitro* and *in vivo* testing of the type described in Section II.C.2. above in order to characterize the inactive ingredients in its product and to demonstrate that those inactive ingredients do not affect the safety or efficacy of the proposed generic drug product. A purported generic product that is not shown, through such *in vitro* and *in vivo* testing, to be formulated with inactive ingredients imparting physicochemical properties designed to impede attempts to manipulate the tablets is of unsafe composition within the meaning of 21 U.S.C. § 355(j)(4)(H) and 21 C.F.R. § 314.127(a)(8)(i).

The statute provides that the safety of inactive ingredients and the composition of a drug product are assessed under the conditions prescribed, recommended, or suggested in the labeling proposed for the drug. 21 U.S.C. § 355(j)(4)(H). Thus, in considering the safety of inactive ingredients and the composition of proposed generic versions of

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[103] *Abbreviated New Drug Application Regulations; Proposed Rule,* 54 Fed. Reg. 28872, 28902-03 (July 10, 1989); *Abbreviated New Drug Application Regulations; Final Rule,* 57 Fed. Reg. 17950, 17969 (April 28, 1992).

[104] Response to Citizen Petition, Docket No. FDA-2009-P-0423 (Feb. 24, 2010), at p. 4, available at: http://www.regulations.gov/#!documentDetail;D=FDA-2009-P-0423-0017. Courts have also acknowledged FDA's discretion on these matters. *See Serono Labs, Inc. v. Shalala,* 158 F.3d 1313, 1326-27 (D.C. Cir. 1998) (rejecting challenge to FDA's conclusions concerning the safety of an inactive ingredient in a proposed generic product, noting the deference warranted on such scientific matters); *Zeneca, Inc. v. Shalala,* 213 F.3d 161, 166-168 (4th Cir. 2000) (deferring to FDA conclusions concerning safety of generic product containing a different preservative).

OxyContin, FDA must consider the analgesic use for which OxyContin is indicated – moderate to severe pain when a continuous around-the-clock analgesic is needed for an extended period of time – rather than any other potential therapeutic uses of the product. Though the labeling for OxyContin warns against all forms of tampering/manipulation, it is both appropriate and imperative that FDA consider these activities when assessing the safety of inactive ingredients in and composition of proposed generic copies. OxyContin is designed and labeled to be taken home and administered in the community. Accordingly, safety for that use – which includes the documented potential for intentional abuse and inadvertent misuse/therapeutic error – necessarily must be taken into account. As the following examples illustrate, FDA has historically and consistently considered abuse and misuse in assessing the safety of drug products under 21 U.S.C. 355, including § 355(e) and §355(d), both of which also address safety under the proposed or approved conditions of use:

- In 1973, the Agency withdrew approval under section 505(e) of the FDCA of all new drug applications for parenteral methamphetamine. While the products were acknowledged to be effective, FDA concluded they were unsafe due to the history of abuse of the products and the associated risk of dependence: "the well-documented history of abuse of parenteral methamphetamine, together with the severe risk of dependence and the presence of effective alternative drugs, creates an unfavorable balance of risk to benefit."[105]

- In 1982, FDA issued a final rule establishing that all camphorated oil drug products were misbranded under section 502 of the FDCA and were new drugs requiring an approved new drug application in order to be marketed. The Agency concluded such products were unsafe due to multiple cases of series illnesses and some deaths following ingestion of these drug products. All of these cases stemmed from misuse, in that camphorated oil drug products had for years been labeled with specific warnings that the products were for external use and were not for ingestion. Affected companies were ordered to recall their products to the retail level.[106]

- In 1997, FDA requested that the sponsors withdraw fenfluramine and dexfenfluramine from the market due to postmarketing reports of heart valve problems in patients taking the drugs in combination with phentermine (*i.e.*, fen-phen and dexfen-phen) for extended periods of time. Neither drug was approved for use in combination with phentermine, and fenfluramine was approved only for short term (a

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[105] *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).

[106] *New Drugs; Camphorated Oil Drug Products for Human Use,* 47 Fed. Reg. 41716 (Sept. 21, 1982).

few weeks) use. Prior to the withdrawals, FDA issued a public health advisory cautioning physicians about the serious safety concerns associated with off-label use of these products.[107]

- In 1998, Duract (bromfenac sodium) Capsules were withdrawn from the market following postmarketing reports of severe liver failure in patients taking the drug for extended periods of time. The labeling provided for use for 10 days or less, but following approval the sponsor and FDA received reports of severe hepatitis and liver failure in patients taking the drug for more than 10 days. Several months prior to the withdrawal, the labeling was revised to include a black box warning against use of the drug for more than 10 days and alerting doctors to the cases of severe hepatits and liver failure. Reports of severe injuries with long term use of Duract continued, so FDA and the sponsor determined that the drug should be withdrawn from the market. The drug no longer appears in the Orange Book.[108]

- In July 2005, FDA requested that Purdue voluntarily suspend sales and marketing of Purdue's approved drug product Palladone® (hydromorphone HCl extended–release) Capsules. At the time, Purdue had begun distribution of the drug only on a very limited basis. FDA's request that Purdue suspend distribution, however, was based on pharmacokinetic data provided to the Agency by Purdue showing that co-ingestion of Palladone with alcohol results in an increase in the peak plasma concentrations of hydromorphone. The labeling for Palladone included strong warnings against co-ingestion of Palladone and alcohol, including a Black Box warning and patient labeling. In addition, in initial distribution, there was no evidence of any such co-ingestion having occurred or having resulted in harm. However, FDA nevertheless concluded that some patients may not comply with the warning against co-ingestion

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[107] Questions and Answers about Withdrawal of Fenfluramine (Pondimin) and Dexfenfluramine (Redux) (9/18/1997), available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm180078.htm; FDA Announces Withdrawal Fenfluramine and Dexfenfluramine (Fen-Phen) (9/15/1997), available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm179871.htm; Public Health Advisory: Reports Of Valvular Heart Disease In Patients Receiving Concomitant Fenfluramine And Phentermine (7/8/1997), available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/PublicHealthAdvisories/ucm180072.htm; "Fen-Phen" Update (Fenfluramine, Phentermine, Dexfenfluramine) (8/27/1997), available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm180082.htm.

[108] FDA Talk Paper, *Wyeth-Ayerst Laboratories Announces the Withdrawal of Duract from the Market* (June 22, 1998), available at: http://www.fda.gov/ohrms/dockets/ac/98/briefingbook/1998-3454B1_03_WL06.pdf.

of Palladone and alcohol (*i.e.,* would use off-label). Therefore, given the potential serious health consequences of opioid overdose (*e.g.,* respiratory depression, coma, death), the Agency determined that the overall risk/benefit profile of Palladone, as formulated, was unfavorable and that distribution of the product should be suspended.[109]

- In 2008, FDA refused to approve a broader indication for Fentora (fentanyl citrate) buccal tablets due to concerns about abuse and misuse. Stating that an expanded indication to include non-cancer patients "may greatly increase the prescribing of this product which may increase the availability of the product for diversion, abuse and misuse, and increase the incidence of accidental exposures which, due to the potency of the product, could potentially have devastating effects," FDA presented the issue to an Advisory Committee.[110] Although the sponsor proposed enhanced risk management activities, including a tightly restricted distribution system, seventeen of the twenty Advisory Committee members voted against approval.[111] FDA later issued a Complete Response letter requesting that the sponsor implement and demonstrate the effectiveness of proposed enhancements to the current Fentora risk management program, and the indication remains limited to opioid tolerant cancer patients with breakthrough pain.[112]

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[109] *See* FDA Asks Purdue Pharma to Withdraw Palladone for Safety Reasons (July 13, 2005), available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2005/ucm108460.htm; http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm129288.htm; Public Health Advisory: Suspended Marketing of Palladone (hydromorphone hydrochloride, extended-release capsules) (7/13/2005), available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/PublicHealthAdvisories/UCM051743; Palladone Package Insert and Medication Guide (2/11/2005), available at: http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=894.

[110] FDA Briefing Package, Joint Meeting of the Anesthetic and Life Support Drugs and Drug Safety and Risk Management Advisory Committees, May 6, 2008, Division Director Memorandum at p. 2, available at: http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4356b2-01-FDA.pdf.

[111] Summary Minutes of the Joint Meeting of the Anesthetic and Life Support Drugs and Drug Safety and Risk Management Advisory Committees (May 6, 2008), available at: http://www.fda.gov/ohrms/dockets/ac/08/minutes/2008-4356m2-final.pdf.

[112] Press Release, *Cephalon Receives Complete Response Letter Regarding Request for Expanded FENTORA Label for Non-Cancer Breakthrough Pain*, (9/15/2008), available at: http://investors.cephalon.com/phoenix.zhtml?c=81709&p=irol-newsArticle&ID=1197029&highlight=; Fentora (fentanyl citrate) buccal tablet label (January 2011), available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021947s013lbl.pdf.

- In 2010, FDA determined that Brevibloc (esmolol HCl) Injection, 250 mg/mL, 10-mL ampule was withdrawn from sale for reasons of safety within the meaning of 21 C.F.R. § 314.161. As a consequence, FDA announced that the product would be removed from the Orange Book and FDA would not accept or approve ANDAs that cite the product as the RLD. FDA's decision rested solely on medication errors, *i.e.*, use of the product in manners inconsistent with labeling. These errors persisted despite labeling revisions intended to reduce the potential for medication errors (e.g., a warning sticker on the product) and Dear Healthcare Professional letters addressing medication errors.[113]

- In 2011, FDA proposed to refuse to approve a supplemental new drug application for a new container size of an ophthalmic drug product containing enough solution to treat both eyes. The basis for the Agency's proposal was the concern that, despite label warnings against touching the dropper tip to any surface, patients may nevertheless touch the dropper tip to the surface of the eye or skin surrounding the eye, thus contaminating the bottle contents. FDA concluded that the proposed larger container size intended for use in both eyes presented the risk of bacteria transmission from one eye to another.[114]

As these examples illustrate, the Agency has routinely considered abuse and misuse when assessing safety under the conditions of use proposed or approved for a drug product. In light of the documented history of abuse and misuse of oxycodone-containing drug products and extended-release opioid drug products, it is essential that the Agency evaluate the potential for abuse and misuse when assessing the safety of inactive ingredients in and composition of proposed generic versions reformulated OxyContin. FDA should refuse to approve any such generic product not shown through *in vitro* and *in vivo* testing described in Section II.C.2. to be of a composition that has physicochemical properties designed to impede attempts to manipulate the tablets, on grounds that the composition of the generic product fails to meet the requirements of 21 U.S.C. § 355(j)(4)(H) and 21 C.F.R. § 314.127(a)(8)(i).

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[113] *Determination that BREVIBLOC (Esmolol Hydrochloride) Injection, 250 Milligrams/Milliliter, 10-Milliliter Ampule, Was Withdrawn from Sale for Reasons of Safety or Effectiveness,* 75 Fed. Reg. 24710. 24711 (May 5, 2010).

[114] *Proposal to Refuse to Approve a Supplemental New Drug Application for Bromday (Bromfenac Opthalmic Solution), 0.09%; Opportunity for a Hearing,* 76 Fed. Reg. 46820, 46821-22 (Aug. 3, 2011).

4. If FDA Declines to Require that ANDAs Include Tamper and Bioavailability Testing Showing Generics Perform As Well As the RLD, Any Products Lacking Such Testing Should Not Be Rated AB To OxyContin

Purdue strongly believes that the Agency should not approve proposed generic products that either have not been subjected to the *in vitro* and *in vivo* testing discussed herein, or that have been tested but do not perform as well as OxyContin. The risks of such products outweigh any potential benefits, and such applications do not satisfy the requirements set forth in Section 505(j) of the Act, as discussed immediately above. However, if the Agency approves an application for any such drug product which might otherwise be considered pharmaceutically equivalent to reformulated OxyContin, it should assign a BX code, indicating that the product is not therapeutically equivalent to OxyContin.[115]

In the 1970s, many states were seeking FDA assistance in preparing formularies for use in identifying which drug products could be substituted for one another. The Agency determined that, rather than responding to individual state inquiries, it was preferable to provide a single list based on common criteria for use by the states. Accordingly, on May 31, 1978, FDA announced that it would provide a list of all prescription drug products that are approved by FDA for safety and effectiveness, along with therapeutic equivalence determinations for multisource prescription products.[116]

FDA's decision to publish such a list, and the procedures the Agency would use in determining therapeutic equivalence and disseminating the list, were explained in preambles to proposed and final rules concerning a change in FDA's public information regulations to reflect availability of the list.[117] The 1979 and 1980 preamables acknowledge that no statute provides for publication of the list or for FDA evaluation of therapeutic equivalence. Instead, the Agency concluded that it was authorized to publish

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[115] An extended-release oxycodone product with tamper resistant attributes that does not perform as well as OxyContin on the *in vitro* and *in vivo* tests discussed in this Petition would raise additional considerations, *e.g.,* the need for additional *in vivo* studies to characterize the performance or desirability of the product following manipulation, the need for post-marketing epidemiologic studies and the need to file and/or consider the application, if at all, under 505(b)(2). This Petition does not address these important considerations.

[116] *Approved Drug Products with Therapeutic Equivalence Evaluations* ("Orange Book"), 32nd Ed. (2012), at Preface, p. iv, available at: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/UCM071436.pdf; *see also Therapeutically Equivalent Drugs,* Proposal, 44 Fed. Reg. 2932, 2934 (Jan. 12, 1979).

[117] *Therapeutically Equivalent Drugs,* Proposal, 44 Fed. Reg. 2932 (Jan. 12, 1979); *Therapeutically Equivalent Drugs; Availability of List,* Final rule, 45 Fed. Reg. 72582 (Oct. 31, 1980).

therapeutic equivalence evaluations based on statutory provisions generally authorizing the dissemination of information.[118] The Agency explained that the list:

> contains only public information and advice. It does not constitute an order or a rule as defined in the Administrative Procedure Act (5 U.S.C. 551(4)) and, consequently, adherence to the rulemaking procedures of that statute (5 U.S.C. 553) is not required. The List neither determines nor adjudicates the legal rights of any drug manufacturer or distributor; it does not impose any requirement or restriction upon any person; it does not interpret or apply the act in a manner that creates any obligation on any person; it makes no recommendation as to which products persons should purchase, prescribe, or dispense, or conversely, which products should be avoided. . . To the extent that the List sets forth FDA's evaluations of the therapeutic equivalence of drug products that have been approved, it contains FDA's advice to the public and to the States regarding an important public health matter. These evaluations do not constitute determinations that any products are in violation of the act or that any products are preferable to others. These are nonregulatory evaluations that are based on the application of certain criteria to information contained in FDA files.[119]

The first publication occurred in October 1980.[120] Thereafter, starting in 1984, the Hatch-Waxman Amendments required FDA to publish a list of drug products approved for safety and effectiveness. 21 U.S.C. § 355(j)(7). Though the Hatch-Waxman Amendments do not provide for publication of therapeutic equivalence evaluations, FDA has continued publication of these evaluations, consistent with the conditions discussed in the 1979 and 1980 Federal Register Notices. Currently, the Orange Book both satisfies the Hatch-Waxman requirement to publish a list of approved drug products and also reflects FDA's therapeutic equivalence determinations.[121]

The concept of therapeutic equivalence used today is the same as that announced in FDA's rulemaking some 30 years ago: "Drug products are considered to be therapeutic equivalents only if they are pharmaceutical equivalents and if they can be expected to have the same clinical effect and safety profile when administered to patients

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118 44 Fed. Reg. at 2936-37; 45 Fed. Reg. at 72584-85.

119 45 Fed. Reg. at 72587; *see also* 44 Fed. Reg. at 2937.

120 Orange Book, Preface, at p. v.

121 "Although not required by the [FDCA], the list, as published also . . . . states therapeutic equivalence evaluations for approved multisource prescription drug products." *Abbreviated New Drug Application Regulations; Proposed Rule,* 54 Fed. Reg. 28872, 28876 (July 10, 1989).

under the conditions specified in the labeling. . . . FDA believes that products classified as therapeutically equivalent can be substituted with the full expectation that the substituted product will produce the same clinical effect and safety profile as the prescribed product."[122]

As explained in the Orange Book, products that meet five general criteria are considered therapeutically equivalent: (1) they are approved as safe and effective; (2) they are pharmaceutical equivalents, meaning they (a) contain identical amounts of the same active drug ingredient in the same dosage form and route of administration, and (b) meet compendial or other applicable standards of strength, quality, purity, and identity; (3) they are bioequivalent, (4) they are adequately labeled; and (5) they are manufactured in compliance with Current Good Manufacturing Practice regulations. [123]

The Orange Book provides that therapeutic equivalence is assessed under the conditions specified in the labeling. Accordingly, an FDA determination that two products are therapeutically equivalent pertains to the approved indications, and does not address other potential therapeutic uses of the products. Though the labeling for OxyContin warns against all forms of tampering/manipulation, the risk of abuse and misuse is nevertheless an unfortunate but unavoidable part of the conditions of use of all controlled substances intended to be taken home and administered in the community. For this reason, as discussed in detail in Section II.C.3.(d) above, FDA must consider the potential for abuse and misuse in assigning therapeutic equivalence evaluations.[124]

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[122] Orange Book, Introduction, Section 1.2, at p. vii; *see* 44 Fed. Reg. at 2937.

[123] Orange Book, Introduction, Section 1.2, at p. vii; *see* 44 Fed. Reg. at 2938-39. "Pharmaceutical equivalents" is formally defined at 21 C.F.R. § 320.1(c).

[124] Even if the Agency determined that the potential for abuse and misuse is not part of the conditions of use of OxyContin, the Agency plainly has authority to consider these activities and determine that a proposed generic product not shown to perform similarly to OxyContin when subjected to *in vitro* and *in vivo* experiments designed to simulate attempts to abuse or misuse the product via tablet manipulation is therapeutically inequivalent to OxyContin. As noted above, therapeutic equivalence evaluations are public information and advice and are not provided for by either statute or regulation. FDA may therefore change the criteria used to evaluate proposed generic versions of innovative products specifically designed to be resistant to tampering, misuse, or abuse. In light of the potential ramifications of filling prescriptions for OxyContin with generic versions lacking physicochemical properties imparting resistance to common forms of tampering (See Section II.C.1. above), FDA must make any change to relevant criteria deemed necessary in order to declare such products to be therapeutically inequivalent. Otherwise, FDA would be taking the risk of affirmatively advocating the unfettered substitution, under existing state laws, of non-tamper-resistant drug products in place of a prescribed product with demonstrated tamper-resistant properties.

FDA's therapeutic equivalence evaluations are designated using particular codes, the meaning of which is defined in the Orange Book.[125] An AB rating signifies FDA's determination that two products are therapeutically equivalent, meaning that the agency believes, based on the data submitted in the ANDA, that the products can be substituted with the full expectation that the substituted product will produce the same clinical effect and safety profile as the prescribed product.[126] An AB rating assigned to a proposed generic version of OxyContin that was not shown, through comprehensive *in vitro* testing and one or more comparative bioavailability studies of manipulated product, to perform as well as OxyContin when subjected to known and anticipated methods of tampering, would be false and misleading. Absent such testing, or in the face of data showing that the proposed generic did not meet the acceptance criteria, there would be no basis on which FDA could conclude that the products have the same safety profile. Under these circumstances, assuming that such a product could ever be approved at all, the appropriate rating is BX, signifying that available data are insufficient to determine therapeutic equivalence, and the products are therefore presumed inequivalent.[127]

III. 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 much harder than conventional tablets, making it difficult to break or crush. Also, the reformulation does not readily dissolve in liquids but, instead, forms a viscous hydrogel that impedes use by nasal or intravenous routes of administration.

An extensive battery of *in vitro* tests designed to simulate attempted tampering showed that reformulated OxyContin is less susceptible to manipulation than the original formulation. *In vivo* pharmacokinetic and abuse potential tests were also conducted to further demonstrate the impact of the reformulation.. From this information, it was

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125 Orange Book, Introduction, Section 1.7, at p. xiii – xx; *see also* CDER Data Standards Manual, Therapeutic Equivalence Code, C-DRG-00701 (Jan. 10, 1995), available at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/DataStandardsManualmonographs/ucm071713.htm.

126 Orange Book, Introduction, Section 1.2, at p. vii; *see* 44 Fed. Reg. at 2937.

127 Orange Book, Introduction, Section 1.2, at p. xx. *See* 44 Fed. Reg. at 2952 (if FDA lacks sufficient data to evaluate whether specific drug products are therapeutically equivalent, FDA will presume the products are inequivalent until adequate info becomes available to make a full evaluation).

apparent before marketing of reformulated OxyContin that the reformulation could have a significant impact on abuse of the drug.

Preliminary data from several epidemiologic studies confirm that the unique physicochemical properties of reformulated OxyContin are in fact having an important impact on abuse and diversion. Specifically, following the introduction of reformulated OxyContin, 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 adverse events involving OxyContin.
- Reduction in unintentional poisonings and adverse events involving OxyContin, including therapeutic errors.

These 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* experiements have predictive value.

Since as early as February 2011, Purdue has received, and continues to receive, Paragraph IV certifications from applicants seeking to market generic versions of reformulated OxyContin. Based on information generally available to Purdue,[128] the company believes that at least some of the proposed generic products are conventional tablet dosage forms readily susceptible to manual crushing and dissolution in small volumes of liquid for purposes of abuse and misuse through oral, nasal, and intravenous routes of administration. Moreover, Purdue has no information suggesting that any of the proposed generic products has been shown through comprehensive *in vitro* experiments and comparative *in vivo* bioavailability studies of manipulated product to duplicate the defining physicochemical features of reformulated OxyContin.

Proposed products that have not been shown through comprehensive, comparative *in vitro* and *in vivo* testing 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

[128] Purdue does not have access to information about these ANDAs which has been designated as highly confidential by the generic applicants and is therefore available only to Purdue's outside patent counsel and one in-house counsel under the strict terms of applicable Protective Orders.

same performance characteristics as reformulated OxyContin. Simply put, such products cannot be "generic" versions of reformulated OxyContin as that term has been used in the almost thirty years since enactment of the Hatch-Waxman amendments. Moreover, as discussed in Section II.C.3. above, applications for such products lack the data required by Section 505(j) of the Act and are unapprovable on multiple grounds.

Given the legal authorities outlined above, and FDA's overarching mission to protect the public health, the Agency ought not to approve a non-tamper-resistant generic version of reformulated OxyContin. FDA should take the actions requested in this Petition in order to properly instruct generic applicants on the requirements applicable to their proposed products and to assure the public that the Agency intends to exercise its authority over these products in a responsible manner.

IV. 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.

V. Economic Impact

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

VI. Certification

I certify that, to my best knowledge and belief: (i) this petition includes all information and views upon which the petition relies; (ii) this petition includes representative data and/or information known to the petitioner that are unfavorable to the petition; and (iii) 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 dates:[129]

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[129] Consistent with the example provided in the preamble to the proposed rule addressing Section 505(q) certifications, specific dates are not provided in this certification for the historical information and FDA precedents referenced herein. *Amendments to Regulations on Citizen Petitions, Petitions for Stay of Action, and Submission of Documents to Dockets*, 77 Fed. Reg. 25, 28 (Jan. 3, 2012). This information generally became known to Purdue employees and representatives on a contemporaneous basis as the referenced events occurred and the referenced findings were made. This historical information, although relied upon as providing part of the factual and legal underpinning for the Agency to take the action requested herein, is not considered to be the type of information covered by the certification requirement of FFDCA Section 505(q). Moreover, a requirement for certification with respect to the dates such

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: Complete Response letter 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.

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information became known to Petitioner would serve no purpose. Any such certification requirement, if applied to any information not specifically addressed in this certification statement, or the refusal by FDA to consider such information in addressing the issues raised herein, would be arbitrary and capricious in violation of the Administrative Procedures Act and the Fifth and Fourteenth Amendments of the United States Constitution and would unconstitutionally burden and infringe upon Petitioner's right to petition the Government, in contravention of the First Amendment of the United States Constitution.

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

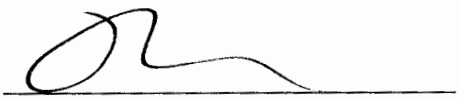
May 10, 2012: First publication (web posting) of *in vivo* data from pharmacokinetic and abuse potential studies of reformulated OxyContin.

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).

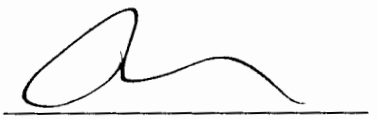
If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: Purdue Pharma L.P.

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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EXHIBITS

Published Abstracts and Posters Describing Epidemiologic Study Results

Poison Center data - American Association of Poison Control Centers

Poison Center data - RADARS®

Diversion Data

Davis, J. *et al., Reduction in Extended Release (ER) Oxycodone Diversion Rates Following The Introduction of A Reformulated ER Oxycodone Product,* International Association for the Study of Pain, 14th World Congress on Pain (August 27-31, 2012), [PF 087] 7

Street Price Data

Severtson, S. G., *et al., Reduced Abuse and Diversion Following the Reformulation of OxyContin®,* RADARS® System 6th Annual Meeting (April 24, 2012) 5

Bucher-Bartelson, B. *et al., A Comparison Of The Street Price Of Original And Reformulated ER Oxycodone,* International Association for the Study of Pain, 14th World Congress on Pain (August 27-31, 2012), [PF 085] 8

Severtson, S. *et al., A comparison of the street price of original and reformulated OxyContin® and immediate release (IR) oxycodone products,* American Pain Society, 31st Annual Scientific Meeting (May 16-19, 2012), Abstract ID # 446 and Poster # 201 9

Substance Abuse Treatment Center – NAVIPPRO®

Chilcoat, H., *et al., Impact of reformulated OxyContin® on rates of abuse through oral and non-oral routes among individuals assessed in substance abuse treatment,* 74th Annual Scientific Meeting of the College on Problems of Drug Dependence, Abstract # 103 and Poster # 68 (presented June 13, 2012) 10

Cassidy, T., *et al., Change in routes of administration for OxyContin and comparators following introduction of reformulated OxyContin® among individuals assessed for substance abuse,* 74th Annual Scientific Meeting of the College on Problems of Drug Dependence, Abstract # 88 and Poster # 66 (presented June 13, 2012) 11

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Black, R. *et al., Effects of reformulated OxyContin® among patients assessed for substance abuse treatment in the NAVIPPRO sentinel surveillance network,* American Pain Society, 31st Annual Scientific Meeting (May 16-19, 2012), Abstract ID # 490 and Poster # 331 13

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Letter to the Honorable Leona Aglukkaq, Minister of Health, Canada, from the Honorable Deborah Matthews, Minister of Health and Long-Term Care, Ontario (June 6, 2012) [Note, Purdue believes this letter may have been misdated and that it may have actually been sent on July 6, 2012 (not June 6). A copy was received by Purdue Pharma L.P. on July 9, 2012] 25

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