



Purdue Pharma L.P.

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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. (hereinafter "Purdue" or "Petitioner"), submits this Citizen Petition pursuant to 21 C.F.R. §§ 10.30, Part 314, and 21 U.S.C. § 355.

I. Action Requested

Petitioner requests that the Food and Drug Administration take the following actions with respect to all New Drug Applications ("NDA") and Abbreviated New Drug Applications ("ANDAs") seeking approval of modified release oral dosage form drug products containing opioid active ingredients:

- (1) Require all applicants to include with their NDAs or ANDAs appropriate data from *in vitro* dissolution tests of all proposed strengths, in solutions containing an appropriate range of concentrations of ethanol ("*in vitro* alcohol data"), and
- (2) If appropriate based on the results of the *in vitro* alcohol data, and other available information, take additional steps to ensure that only those products with a favorable risk/benefit profile are approved. In appropriate circumstances, such additional steps would include, for example, requiring use of risk minimization tools (e.g., enhanced label warnings, patient educational materials, or restricted distribution); requiring additional *in vitro* and/or *in vivo* studies; or refusing to approve the application.

II. Statement of Grounds

A. Background: FDA's Request For The Withdrawal Of Palladone Established The Critical Importance of Alcohol-Interaction Of Modified Release Opioid Drug Products

In July 2005, FDA requested that Purdue voluntarily suspend sales and marketing of Purdue's approved drug product Palladone® (hydromorphone HCl extended-release) Capsules. FDA's request was based on extensive review of 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. Specifically, under fasted conditions, co-ingestion of a 12 mg Palladone capsule with 8 ounces of 40% (80 proof) alcohol resulted in average peak hydromorphone concentrations approximately 6 times greater than when the product is taken with water, with individual patients showing concentrations 16 times greater. In the fed state, average peak hydromorphone concentrations were approximately 3.5 times greater than when the product is taken with water. Purdue's data further indicated that co-ingestion of Palladone, 12 mg with 8 ounces of 20% and 4% alcohol also increased peak plasma concentrations of hydromorphone, when compared with co-ingestion with water.¹

Although Purdue had submitted these pharmacokinetic data to FDA prior to marketing Palladone and had significantly enhanced the always present warnings against ingestion of alcohol while using Palladone,² FDA nevertheless

¹ The Agency's public pronouncements and its summary of Purdue's data are available at: <http://www.fda.gov/cder/drug/infopage/palladone/default.htm>

² The Palladone labeling utilized at the time of the product launch included several strong warnings against co-ingestion of Palladone and alcohol, including a Black Box warning. *See, e.g.*, Palladone Labeling (11/17/2004), attached hereto as Exhibit A ("Consuming alcohol while taking Palladone™ Capsules or taking broken, chewed, dissolved, or crushed Palladone™ Capsules or its contents can lead to the rapid release and absorption of a potentially fatal dose of hydromorphone," "Consuming alcohol while taking Palladone Capsules can cause significant increases in peak hydromorphone concentrations," "Breaking, crushing, chewing, or dissolving the contents of a Palladone™ Capsule or consuming alcohol while taking Palladone Capsules can result in the uncontrolled delivery of the opioid and poses a significant risk of overdose and death (see **WARNINGS** and **DRUG ABUSE AND ADDICTION**)," "Hydromorphone may be expected to have additive effects, when used in conjunction with alcohol, other opioids, or drugs, whether legal or illicit, which cause central nervous system depression. Additionally, consuming alcohol while taking Palladone Capsules can cause significant

believed that some patients may not comply with the warning against co-ingestion of Palladone and alcohol.³ In connection with a later meeting of the Advisory Committee for Pharmaceutical Science, FDA explained that its belief that some patients may not heed alcohol warnings was based in part on survey data showing that patients with chronic low back pain using opioid drugs continue to drink alcohol, despite current warnings against co-ingestion of opioids and alcohol.⁴ 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.⁵

As FDA explained in the Questions and Answers released with the Public Health Advisory,⁶ at the time Palladone was approved, FDA had *in vitro* data showing that alcohol could accelerate the release of hydromorphone from Palladone capsules, but neither FDA nor Purdue anticipated the *in vivo* effects shown in Purdue's later pharmacokinetic study.

increases in peak hydromorphone concentrations,” “Patients should be instructed not to consume alcohol while taking Palladone Capsules.” “Patients should NOT combine Palladone™ Capsules with alcohol,” “Do not drink alcohol while taking Palladone Capsules”).

³ See Palladone (hydromorphone hydrochloride extended release) Capsules Questions and Answers, available at: <http://www.fda.gov/cder/drug/infopage/palladone/palladoneQA.htm>

⁴ See October 26, 2005 Transcript, p. 41, available at: <http://www.fda.gov/ohrms/dockets/ac/05/transcripts/2005-4187T2.pdf> and Briefing Materials, available at: http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4187B1_01_08-Alcohol-Induced.pdf

⁵ See Palladone (hydromorphone hydrochloride extended release) Capsules Questions and Answers, available at: <http://www.fda.gov/cder/drug/infopage/palladone/palladoneQA.htm> and FDA Alert for Healthcare Professionals, Hydromorphone Hydrochloride Extended Release Capsules (marketed as Palladone™), available at: <http://www.fda.gov/cder/drug/InfoSheets/HCP/hydromorphoneHCP.pdf>

⁶ See Palladone (hydromorphone hydrochloride extended release) Capsules Questions and Answers, available at: <http://www.fda.gov/cder/drug/infopage/palladone/palladoneQA.htm>

B. The Agency Has Acknowledged The Need For A Consistent Regulatory Approach To Assessing Alcohol-Induced Dose Dumping

Three months after the withdrawal from the market of the Palladone capsule formulation, FDA discussed its approach to mitigating the risks of alcohol-induced dose dumping with the Advisory Committee for Pharmaceutical Science.⁷ The Agency explained that the recent experience with Palladone:

necessitates development of a general regulatory approach to address the issue of whether alcohol undermines the release characteristics of the drug for new drug applications and currently marketed products that utilize a controlled-release mechanism. The goal of the regulatory approach should be to minimize the risk of alcohol-induced dose dumping from modified-release dosage forms, irrespective of any warnings on product labeling and instructions by health care providers.⁸

At the Advisory Committee meeting, the Agency outlined its approach to already-approved products, which entailed prioritization of products based on the characteristics of the drug and patient population, *in vitro* testing by FDA and, if warranted, *in vivo* testing by the sponsor. If *in vivo* data confirms the existence of a drug-alcohol interaction, the Agency stated it would consider various regulatory options, including changes in labeling, including a patient medication guide, other formal risk minimization plans, such as restricted access, or withdrawal of the drug product.⁹

⁷ See Briefing Materials, available at: http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4187B1_01_08-Alcohol-Induced.pdf and October 26, 2005 Transcript, pp. 9 - 55, available at: <http://www.fda.gov/ohrms/dockets/ac/05/transcripts/2005-4187T2.pdf>

⁸ See Briefing Materials, available at: http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4187B1_01_08-Alcohol-Induced.pdf

⁹ October 26, 2005 Transcript, pp. 13-16, available at: <http://www.fda.gov/ohrms/dockets/ac/05/transcripts/2005-4187T2.pdf> FDA has not publicly discussed the current status of its efforts to assess already-marketed modified release drug products for drug-alcohol interactions. While the focus of this Petition is on products not yet approved by the Agency, we fully support the Agency's efforts to characterize and address drug-alcohol interactions among marketed products and urge the Agency to prioritize this important activity.

With respect to new modified release drug products, the Agency indicated that *in vitro* alcohol testing during drug development is advisable. Depending on therapeutic considerations, the Agency may determine that certain types of alcohol-drug interactions are unacceptable for certain drug products and refuse to approve formulations exhibiting alcohol-drug interactions.¹⁰

Despite the seemingly proactive approach initiated immediately after the withdrawal of Palladone, FDA has not announced any generally applicable requirements for *in vitro* or *in vivo* data assessing the potential for alcohol-drug interactions, or published any guidance on the subject. Alcohol-induced dose dumping was to be discussed at a May 2007 meeting of the Advisory Committee for Pharmaceutical Science and Clinical Pharmacology, but the meeting was canceled and no details on the planned discussion have been released.¹¹ This subject does not appear on FDA's most recent regulatory agenda¹² and the Agency has not indicated when information on the Agency's policies might be publicly disclosed.

Based on publicly available information, it appears that FDA has, instead, evaluated potential alcohol-drug interactions on a case-by-case basis. For example, in June 2006, FDA approved Opana® ER (oxymorphone hydrochloride) extended-release tablets. The label includes a description of an *in vivo* study examining the effect of alcohol (40%, 20%, 4%, and 0%) on the bioavailability of a single dose of 40 mg Opana ER, as well as strong warnings against co-ingestion of alcohol with Opana ER.¹³

Moreover, in response to a Citizen Petition concerning approval requirements applicable to ANDAs for generic versions of Wellbutrin XL (bupropion HCl extended release tablets), the Agency stated that it had required *in vitro* alcohol testing:

¹⁰ October 26, 2005 Transcript, pp. 16-17, available at: <http://www.fda.gov/ohrms/dockets/ac/05/transcripts/2005-4187T2.pdf> and Slide Presentation by Robert J. Meyer, MD, *Clinical Relevance of Alcohol-Induced Dose Dumping*, available at: http://www.fda.gov/ohrms/dockets/ac/05/slides/2005-4187S2_01_Meyer.ppt

¹¹ See 72 Fed. Reg. 12621 (March 16, 2007); 72 Fed. Reg. 16797 (April 5, 2007).

¹² Unified Agenda of Federal Regulatory and Deregulatory Actions, Spring 2007, available at: <http://www.fda.gov/oc/industry/unifiedagenda/spring2007.html>

¹³ See <http://www.fda.gov/cder/foi/label/2006/021610s001,021611s0011bl.pdf>

FDA asked ANDA applicants for generic bupropion HCl extended release tablets to submit data from *in vitro* dissolution studies using various concentrations of ethanol in the dissolution medium to evaluate the possible interaction between alcohol and the excipients in both Wellbutrin XL and generic bupropion HCl extended-release tablets. FDA will evaluate the results of the *in vitro* data submitted by the ANDA applicants and consider these results when determining whether to approve each ANDA.¹⁴

While these examples indicate that the Agency has, at times, considered the possibility of alcohol-induced dose dumping, there is no indication that the Agency has adopted a systematic approach to all drug products presenting similar potential risks.

C. Drug-Alcohol Interactions And Associated Serious Health Consequences Attributable To Opioid Overdose Potentially Impact All Modified Release Opioids

At the time the Agency announced the voluntary withdrawal of Palladone, it also stated, "FDA continues to investigate other long-acting pain relief drug products for possible dose-dumping when taken with alcohol."¹⁵ During the same time period, the Agency conducted *in vitro* tests on at least two modified release opioid products – Kadian® (morphine sulfate extended release capsules) and Avinza® (morphine sulfate extended release capsules) – and requested label changes based on those data.¹⁶ Similarly, just weeks after the withdrawal of

¹⁴ See Response to Citizen Petition, Docket No. 2005P-0498 (Dec. 14, 2006), available at: <http://www.fda.gov/ohrms/dockets/dockets/05p0498/05p-0498-pav0001-vol1.pdf>

¹⁵ See Palladone (hydromorphone hydrochloride extended release) Capsules Questions and Answers, available at: <http://www.fda.gov/cder/drug/infopage/palladone/palladoneQA.htm>

¹⁶ See July 22, 2005 Alpharma Inc. Press Release, *Alpharma to Change Kadian® Labeling*, available at: <http://www.alpharma.com/pages/getpage.aspx?id=19D731C5-5017-4DF9-9A67-4F514C00B9DF> and Letter to Ligand Pharmaceuticals, Inc. from B. Rappaport (Oct. 18, 2005), and accompanying label, available at: <http://www.fda.gov/cder/foi/appletter/2005/021260s006ltr.pdf> and <http://www.fda.gov/cder/foi/label/2005/021260s006lbl.pdf> Ultimately, Alpharma provided FDA with *in vivo* data, which the Agency concluded demonstrated that there is not an interaction between Kadian and alcohol *in vivo* when co-administered. See Letter

Palladone, Health Canada issued an Advisory stating that it had requested that all manufacturers of modified release opioids submit data on the interaction of their products with alcohol, due to the possibility that other products in this class exhibit drug-alcohol interactions similar to those exhibited by Palladone:

Potentially fatal interaction between slow-release Opioid painkillers and alcohol. . . , Health Canada is advising Canadians of serious health risks when consuming alcohol while taking any type of slow-release painkillers known as opioids. These medications are used for the relief of severe pain over a prolonged period of time. . . . This safety issue may be limited to Palladone XL, but patients using other slow-release opioid products should be aware that there may be a possibility that these products could react in the same way when taken with alcohol. . . . To determine whether this effect might occur with slow-release drugs other than Palladone XL, Health Canada is requesting that all manufacturers of these drugs provide data on the interaction of their product with alcohol. If they cannot do so, they will be asked to conduct studies on product interaction with alcohol, and these studies are expected to be completed within six months.¹⁷

As noted above, approximately a year after the withdrawal of Palladone from the U.S. market, FDA approved Opana® ER (oxymorphone hydrochloride) extended-release tablets with labeling describing data from an *in vivo* alcohol-drug interaction study and including strong warnings against co-ingestion of alcohol with Opana ER.

Recently, Purdue has also determined that a generic controlled release oxycodone product, manufactured by Cimex Pharma AG and sold by generic companies in Germany, rapidly dissolves in the presence of alcohol. Purdue's independent associated company Mundipharma conducted *in vitro* tests on the Cimex product sold by Stada Arzneimittel AG. These data show that dissolution of the Stada/Cimex product is significantly accelerated in dissolution media containing varying concentrations of alcohol.¹⁸ These data have been shared

to Alpharma Pharmaceuticals, Inc. from B. Rappaport (Feb. 27, 2007), available at: <http://www.fda.gov/cder/foi/applletter/2007/020616s017,%20s021ltr.pdf>

¹⁷ See Advisory 2005-84, *Potentially fatal interaction between slow-release Opioid painkillers and alcohol*, available at: http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2005/2005_84_e.html

¹⁸ See *The Effect of Ethanol on the In-Vitro Dissolution Rate of Oxycodone-HCl STADA® PR Tablets*, attached hereto as Exhibit B. The product is currently sold in

with European authorities. Thus far, enhanced warnings have been required on the Cimex manufactured products, and additional actions are under consideration.

The Opana ER and generic oxycodone data confirm what both FDA and Health Canada understood at the time Palladone was withdrawn – all modified release opioid drugs, not just Palladone or hydromorphone, can be formulated so that they dose dump when exposed to alcohol, and the consequences of such dumping warrant consistent, class-wide action to assure proper design, formulation, testing, labeling, and risk minimization strategies are employed to control this risk.

D. A Class Wide Requirement For *In Vitro* Alcohol Testing Is An Appropriate Regulatory Response To Address The Potentially Serious Consequences Of Alcohol-Induced Dose Dumping By Modified Release Opioid Drug Products

The key concerns driving FDA's response to the Palladone data, namely, (a) failure of some patients to avoid alcohol while taking opioid drugs, despite strong label warnings, and (b) the potential serious health consequences of overdose (e.g., respiratory depression, coma, death), are not unique to Palladone or hydromorphone, and instead apply to the entire class of modified release opioid drug products. It is therefore essential that the Agency evaluate potential alcohol-drug interactions before approving any new products in this class.

A requirement that all NDAs and ANDAs for modified release opioid drug products include appropriate *in vitro* alcohol data would not be unduly burdensome on sponsors, as the tests are neither costly nor time consuming. Such a requirement is also consistent with the approach FDA outlined at the 2005 Advisory Committee meeting.¹⁹

Germany by Novartis AG, STADA Arzneimittel AG, Betapharm Arzneimittel GmbH, and Ratiopharm GmbH.

¹⁹ The concerns expressed by the Agency at the 2005 Advisory Committee meeting were not limited to opioid drug products and, indeed, properly extend to other classes of modified release narrow-therapeutic-range drugs or other drugs that exhibit synergistic or additive effects when co-administered with alcohol. By focusing on the need for alcohol-interaction testing of modified release opioid drug products, this Petition is not intended to suggest that such testing is not also warranted for other categories of drugs. However, because FDA has already made the determination that alcohol-interaction with modified release opioid drug products presents significant potential public health risks, additional scientific or medical consideration should not be necessary before that determination is

These *in vitro* data, along with any other available information (e.g., on the modified release mechanism) should then be used by the Agency to determine whether additional steps are necessary to ensure only those products with a favorable risk/benefit profile are approved. These additional steps could include requiring use of the risk minimization tools discussed in FDA's RiskMAP Guidance.²⁰ For example, FDA could require additional *in vitro* and/or *in vivo* studies to further characterize the effects of alcohol on dissolution and absorption of the product. In appropriate circumstances, FDA could require enhanced warnings in professional and patient labeling, distribution of patient educational materials, or restricted distribution.²¹ When the test data warrant, FDA could and should refuse to approve applications.²²

E. FDA Requirements And Approval Criteria Must Be Consistent

We are not aware of any effort by the Agency internally to assure that all modified release opioid drug products are consistently screened for their potential alcohol interaction risks. Such efforts are necessary to protect the public health, and are also mandated by the Administrative Procedure Act. See *Bracco Diagnostics, Inc. v. Shalala*, 963 F.Supp. 20 (D.D.C. 1997) (failure to subject similarly situated products to consistent standards and procedures is arbitrary and capricious in violation of the APA); see also *Allergan, Inc. v. Shalala*, 1994 U.S. Dist. LEXIS 21716 (D.D.C. Nov. 10, 1994). In addition, although the regulatory pathways for NDA and ANDA approvals are different and, thus, so are the options for addressing alcohol-interaction issues identified in testing of NDA and ANDA products, every modified release opioid drug product submitted to the Agency for approval presents the same potential risk, which should be subjected to the same test procedures.

properly and consistently applied to all modified release opioid drug products, however they may be filed for approval before the Agency.

²⁰ *Guidance for Industry: Development and Use of Risk Minimization Action Plans* (March 2005), available at: <http://www.fda.gov/cder/guidance/6358fnl.pdf>

²¹ Enhanced risk minimization strategies, labeling or distribution restrictions are not options in the case of products that are the subject of ANDAs. Such products are generally required to carry the same labeling as the reference listed drugs (RLD) on which the application is based. Thus, in the case of ANDAs, where testing shows a greater risk of alcohol interaction than with the RLD, the applications are simply unapprovable.

²² Sponsors, of course, would always have the option of seeking to reformulate their products so as to reduce any drug-alcohol interaction.

In order to help assure effective and consistent evaluation of these risks, the application of *in vivo* alcohol test requirements for modified release opioid drug products should not depend on *ad hoc* or case-by-case evaluations or ambiguous (or non-existent) internal communication between offices at FDA responsible for reviewing and approving different types of applications. Two years after the voluntary withdrawal of Palladone from the market, it is time for the agency to adopt a clear and unambiguous *in vitro* test requirement that can help prevent dose-dumping products (*e.g.*, the Cimex product in Germany) from obtaining approval for marketing in the United States.

III. 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.

IV. Economic Impact

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

V. Certification

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

VI. Conclusion

All modified release opioid drug products can be formulated so that they dose dump when exposed to alcohol, and all present serious risks in the case of overdose. In connection with its review of Purdue's Palladone data, FDA has already made the determination that some patients who take opioid drugs continue to drink alcohol, despite strong label warnings. Thus, the potential for alcohol-induced dose dumping and resulting overdose requires consistent, class-wide action to assure proper design, testing, labeling, and risk minimization strategies are employed to control this risk.

Purdue therefore requests that the Agency:

- (1) Require all applicants seeking approval of modified release oral dosage form drug products containing opioid active ingredients

include with their NDAs or ANDAs appropriate data from *in vitro* dissolution tests of all proposed strengths in solutions containing an appropriate range of concentrations of ethanol, and

- (2) If appropriate based on the results of the *in vitro* alcohol data, and other available information, take additional steps to ensure that only those products with a favorable risk/benefit profile are approved for sale.

Respectfully submitted,



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