DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
10903 New Hampshire Avenue
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SEP 10 2013

Kirk W. Van Rooyan, MD
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Re: Docket No. FDA-2005-P-0325[1]

Dear Dr. and Mrs. Van Rooyan:

This letter responds to your citizen petition, received February 17, 2005 (Petition), which expresses concern about the abuse potential of OxyContin (oxycodone hydrochloride), its generic equivalents,[2] and Palladone (hydromorphone hydrochloride). In the Petition, you request that the Food and Drug Administration (FDA or the Agency): (1) "temporar[il]y recall[3] [the] approval" of both OxyContin (and its generic equivalents) and Palladone, and remove these products from the market until they are chemically reformulated by their manufacturers to have "minimal abuse potential;" and (2) change the labeling for these drugs to limit their approved indication for use to the treatment of "severe chronic pain from documented peripheral tissue disease processes" (Petition at 1).[4] Your request is based on your view that there is "insufficient scientific evidence that sustained release opioids offer the improved efficacy over immediate release forms to justify the increased risk" (Petition at 8), and that "[n]umerous reports from across the country of death and addiction caused by OxyContin clearly document a national problem of escalating opioid abuse, diversion, and inappropriate physician prescribing" (Petition at 2).

FDA has carefully reviewed your Petition and the comments submitted to the Petition docket. As described more fully below, the Petition is granted in part and denied in part. Specifically, the Agency grants your request to withdraw approval of OxyContin to the extent that the original formulation of OxyContin (NDA 20-553) (original OxyContin) has been voluntarily withdrawn from sale and FDA has determined that it was withdrawn for reasons of safety and effectiveness. The remaining requests in your Petition are denied. However, as part of FDA's ongoing efforts to help ensure the safe use of opioids, we have notified application holders for extended-release/long-acting (ER/LA) opioid

[1] The Petition originally was assigned docket number 2005P-0076. This number has been changed to FDA-2005-P-0325 as a result of FDA's transition to its new docketing system (Regulations.gov) in January 2008.

[2] The informal term "generic" refers to a drug that has been shown to have the same active ingredient, dosage form, strength, route of administration, labeling, and conditions of use, among other characteristics, as a reference listed drug (RLD), and is bioequivalent to the RLD. *See* section 505(j)(2)(A) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 355(j)(2)(A)).

[3] We interpret your request for a "temporary recall of approval" to mean withdrawal of approval of the NDAs for OxyContin and Palladone and removal from the market.

[4] You also suggest using the following terminology in the indication: "severe pain attributable to medically documented tissue disease processes" (Petition at 7-8).

analgesics, including drugs containing oxycodone and hydromorphone, of necessary safety labeling changes and postmarketing study requirements. As with all FDA-approved drugs, FDA will continue to monitor and review available safety information related to ER/LA opioids and take regulatory action as appropriate.

I. BACKGROUND

A. OxyContin

At the time your Petition was submitted, the proprietary name *OxyContin* referred to Purdue Pharma's oxycodone hydrochloride (oxycodone) extended-release (ER) tablet that was the subject of new drug application (NDA) 20-553. FDA approved original OxyContin on December 12, 1995, for "the management of moderate to severe pain where use of an opioid analgesic is appropriate for more than a few days." The indication for OxyContin subsequently was revised to state: "for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time."[5]

During the years following the approval of original OxyContin, abuse of prescription opioid products became a growing public health problem in the United States. Original OxyContin was among this group of increasingly abused drugs.

Purdue Pharma subsequently submitted and received approval of another new drug application, NDA 22-272, for a reformulated version of OxyContin (reformulated OxyContin) on April 5, 2010. Like original OxyContin, reformulated OxyContin was approved for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. A short time later, Purdue Pharma voluntarily withdrew original OxyContin from sale.

On April 16, 2013, FDA approved revised labeling regarding the abuse-deterrent properties of reformulated OxyContin based on a careful assessment of available data. The revised labeling states that the product has physical and chemical properties that are expected to make abuse via injection difficult and to reduce abuse via the intranasal route (i.e., snorting).[6] FDA also determined that original OxyContin was withdrawn from marketing for reasons of safety or effectiveness.[7] The Agency concluded that, relative to reformulated OxyContin, original OxyContin provides the same therapeutic benefit, but poses an increased potential for abuse by certain routes of administration.[8] FDA determined that, based on the totality of the data and information available to the agency, the benefits of the original OxyContin formulation no longer outweighed its risks. Consequently, FDA will not accept or approve abbreviated new drug applications

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[5] *See* OxyContin (NDA 20-553) labeling approved July 18, 2001. The basis for your assertion that Purdue Pharma was "allowed to extend its indications to moderate pain situations" two years after approval (Petition at 6) is unclear.

[6] *See* www.accessdata.fda.gov/drugsatfda_docs/label/2013/022272Orig1s014lbl.pdf.

[7] *See* 78 Fed. Reg. 23273 (April 16, 2013).

[8] *Id.*

(ANDAs) that refer to original OxyContin. FDA formally withdrew approval for the original OxyContin NDA on August 7, 2013.[9]

B. Palladone

Palladone (hydromorphone hydrochloride) (NDA 21-044) was approved on September 24, 2004. Palladone ER capsules were indicated for use in opioid-tolerant patients for "the management of persistent, moderate to severe pain in patients requiring continuous, around-the-clock analgesia with a high potency opioid for an extended period of time (weeks to months) or longer."[10] As with all ER/LA opioids, Palladone's labeling includes a boxed warning about such issues as respiratory depression and the dangers of taking broken, chewed, dissolved, or crushed capsules, among others.[11] Shortly after Palladone's approval, however, it was determined that "dose dumping"—rapid release of the entire dose of the drug—could occur when Palladone was taken with alcohol, thus increasing the risk of harm from overdose of hydromorphone.[12] In light of this safety concern, Purdue Pharma, the NDA holder, voluntarily agreed to suspend all sales and marketing of the drug in July 2005.[13] Palladone has not been marketed since that time.

In part because of the concerns identified with Palladone, FDA now requires that new ER/LA opioids demonstrate that they do not present alcohol-related overdose risks, such as those associated with Palladone.[14] Since Palladone was withdrawn from the market, all NDAs for ER/LA opioids have been required to include studies assessing whether concomitant alcohol use results in loss of the extended-release characteristics of the product.[15] The required studies include in vitro dissolution studies, and, if the results of these studies warrant it, an in vivo pharmacokinetic study.[16]

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[9] *See* www.gpo.gov/fdsys/pkg/FR-2013-08-07/pdf/2013-18694.pdf.

[10] Palladone Labeling (Boxed Warning), available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2004/021044lbl.pdf.

[11] *See* http://www.accessdata.fda.gov/drugsatfda_docs/label/2004/021044lbl.pdf.

[12] *See, e.g.*, http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/PublicHealthAdvisories/ucm051743.htm; and http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm129288.htm.

[13] *Id.*

[14] *See, e.g.*, 21 CFR 320.25(f)(1)(ii) ("The purpose of an in vivo bioavailability study involving a drug product for which an extended release claim is made is to determine if . . . [among other things,] [t]he bioavailability profile established for the drug product rules out the occurrence of any dose dumping").

[15] *See, e.g.*, *Draft Guidance on Oxycodone Hydrochloride*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM220198.pdf.

[16] On March 1, 2010, FDA approved Exalgo (hydromorphone hydrochloride) ER tablets (NDA 21-217). Although, like Palladone, Exalgo is an ER/LA hydromorphone product, the in vitro and in vivo studies submitted in support of the Exalgo NDA showed that the drug maintained its controlled-release property even when taken with alcohol. Exalgo thus has no known alcohol-related risk of dose dumping, and therefore, lacks the risk that prompted Palladone's withdrawal from the market. Exalgo, like other ER/LA opioids, is subject to the shared-system ER/LA Opioid Analgesic REMS and the proposed labeling changes discussed in this response.

C. Balancing the Benefits and Risks of ER/LA Opioids

FDA acknowledges that ER/LA opioid abuse and misuse are serious public health problems. The Agency is actively involved in ongoing efforts to curb the abuse of prescription drugs, particularly ER/LA opioids. For example, in January 2010, FDA published a draft guidance entitled "Assessment of Abuse Potential of Drugs."[17] The draft guidance provides a definition of abuse potential; information on submitting an abuse potential assessment, including a proposal for scheduling; a description of what constitutes an adequate abuse potential assessment; and information for application holders performing an assessment, including (1) the design and conduct of appropriate studies and investigations and (2) recommendations for submitting a proposal for scheduling. In addition, in January 2013, FDA issued a draft guidance entitled "Abuse-Deterrent Opioids—Evaluation and Labeling,"[18] which, when finalized, will explain FDA's current thinking about the studies that should be conducted to demonstrate that a given formulation has abuse-deterrent properties, how those studies will be evaluated, and what labeling claims may be approved based on the results of those studies.[19]

FDA has also held Advisory Committee meetings regarding product-specific properties intended to deter abuse and misuse. For example, the Agency held a Joint Meeting of the Anesthetic and Life Support Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee on October 21 and 22, 2010, to discuss considerations for the design of post-marketing studies for reformulated OxyContin tablets (NDA 22-272, discussed above), and for Embeda (morphine sulfate ER capsules with sequestered naltrexone hydrochloride) (NDA 22-321).[20] As noted above, in April 2013 FDA approved revised labeling for reformulated OxyContin that describes the drug's abuse-deterrent properties and explains its reduced potential for certain route-specific methods of abuse.[21]

FDA approved a shared-system Risk Evaluation and Mitigation Strategy (REMS) for ER/LA opioids on July 9, 2012 (ER/LA Opioid Analgesic REMS).[22] The goal of the ER/LA Opioid Analgesic REMS is to "reduce serious adverse outcomes resulting from

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[17] A copy of the draft guidance is available on our website at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf.

[18] Available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM334743.pdf.

[19] *Id.* at p. 1.

[20] The transcript and other materials from the meeting are available on FDA's website at: http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/ucm199874.htm.

[21] *See* OxyContin (oxycodone hydrochloride) extended-release tablets, NDA 022272 Labeling, available at www.accessdata.fda.gov/drugsatfda_docs/label/2013/022272Orig1s014lbl.pdf.

[22] *See* www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM311290.pdf (most recently modified in April, 2013).

inappropriate prescribing, misuse, and abuse of [ER/LA opioids] while maintaining patient access to pain medications."[23] Under the ER/LA Opioid Analgesic REMS, "[a]dverse outcomes of concern include addiction, unintentional overdose, and death."[24] The ER/LA Opioid Analgesic REMS is currently limited to ER/LA opioid products because FDA has concluded that there are disproportionate safety concerns associated with these products compared to immediate-release (IR) opioids.[25]

Currently, more than 30 products are subject to the ER/LA Opioid Analgesic REMS.[26] The ER/LA Opioid Analgesic REMS contains requirements for distribution of a Medication Guide with each prescription filled, as well as a requirement that training be made available to all those who prescribe ER/LA opioids. Prescriber education training is considered ER/LA Opioid Analgesic REMS-compliant if, among other things, it includes the elements described in the "FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics" (FDA Blueprint).[27] The FDA Blueprint provides guidance to prescribers to enable appropriate ER/LA opioid prescribing practices, as well as information prescribers can use in counseling patients about the risks and benefits of ER/LA opioid use.

II. DISCUSSION

A. Request That FDA Withdraw Approval of Original OxyContin, Generics to Original OxyContin, and Palladone Until They Can Be Reformulated to Be of "Minimal Abuse Potential"

You request that FDA withdraw the approval of "OxyContin (and generic equivalents)"[28] and of Palladone until these products have been chemically reformulated to be of "minimal abuse potential" (Petition at 1). In support of the above request, you note considerable increases in the abuse of oxycodone drugs, including original OxyContin, in the years prior to submission of the Petition (Petition at 2-4). You state that both original OxyContin and Palladone are readily available from internet pharmacies, and that both easily can be converted from ER tablets to single, large IR doses (Petition at 4). You also

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[23] *Id.* at p. 2.

[24] *Id.*

[25] *See* http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm309742.htm#Q5; *see also, e.g.*, Dormitzer, C. Opioid Abuse and Misuse: Data from the National Survey on Drug Use and Health and the Drug Abuse Warning Network. Joint Meeting of the Anesthetic and Life Support Drugs Advisory Committee (ALSDAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM). UMUC Inn and Conference Center by Marriott, Adelphi, MD, July 22-23, 2010 (available at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM220950.pdf) (providing data showing growing harm associated with ER/LA opioids).

[26] The list of drugs required to have a REMS, grouped by application holder, may be found at www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM348818.pdf.

[27] Available at http://www.fda.gov/downloads/drugs/drugsafety/informationbydrugclass/ucm277916.pdf.

[28] Because your petition references NDA 20-553 and was submitted before FDA approved reformulated OxyContin, we assume that your request for withdrawal pertains to original OxyContin rather than reformulated OxyContin.

raise concerns about accidental overdoses by patients to whom these drugs are prescribed (Petition at 4), concerns that were echoed in some of the comments to the Petition.[29]

Since your Petition was submitted, both original OxyContin and Palladone have been withdrawn from marketing, and approval of the NDA for original OxyContin has been withdrawn. (There were no approved generic versions of original OxyContin or Palladone, so there were no generic products or approved ANDAs to withdraw.) Because FDA has determined that original OxyContin was withdrawn for reasons of safety and effectiveness in light of the availability of the new abuse-deterrent formulation of reformulated OxyContin, no generic versions of original OxyContin can be approved. Therefore, the Agency grants your request to withdraw approval of OxyContin to the extent that original OxyContin has been voluntarily withdrawn from sale and FDA has determined that it was withdrawn for reasons of safety and effectiveness, and to the extent that FDA announced withdrawal of approval of the NDA on August 7, 2013. Your requests are otherwise denied, for the reasons discussed below.

1. A "Minimal Abuse Potential" Standard is Not Feasible

The Petition does not define the phrase "minimal abuse potential," and thus, it is unclear what scientific evidentiary threshold you believe should be applied. Under FDA's interpretation of the term, however, as described below, "minimal abuse potential" is not an achievable characteristic for the active ingredients at issue here.

Oxycodone and hydromorphone are listed under Schedule II of the Controlled Substances Act[30] because they "have a high potential for abuse which may lead to severe psychological or physical dependence."[31] For example, in addition to their pain-relieving effects, opioid drugs often induce feelings of euphoria, which is a sensation some opioid users may enjoy enough to abuse the drugs. FDA does not currently believe there is any current method that can be applied to a Schedule II opioid analgesic that will result in a product with "minimal abuse potential," regardless of formulation or tamper-resistance design.[32] However, if FDA were to withdraw the NDAs of all drugs with greater-than-minimal abuse potential, there would be no opioid drugs, ER/LA or IR, available to patients for pain relief.[33] Such an outcome would result in an unacceptable setback for

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[29] *See* docket nos. FDA-2005-P-0325-0010 and FDA-2005-P-0325-0013.

[30] See 21 U.S.C. 801 *et seq.*; 21 CFR 1308.12(b)(1)(vii) and (xiii).

[31] http://www.deadiversion.usdoj.gov/schedules/index.html.

[32] FDA cautions that existing technologies "have not yet proven successful at deterring the most common form of abuse – swallowing a number of intact pills or tablets to achieve a feeling of euphoria. Because opioid analgesics must be able to deliver the opioid to patients for the management of pain, the extent to which an abuse-deterrent product is able to reduce abuse will never be absolute." Draft Guidance for Industry, *Abuse-Deterrent Opioids—Evaluation and Labeling* (available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM334743.pdf), p. 2.

[33] You paraphrase one of Purdue Pharma's arguments as, "Purdue claims that if OxyContin and Palladone are removed from the market, there would be no reason not to take other oral opioids off the market as well." Docket No. FDA-2005-P-0325-0012, Response to comments submitted to the docket by Purdue Pharma (Van Rooyan Response) at 6-7. You then respond by asserting that the strengths of original

public health, because opioid drugs are a critical tool in managing pain and relieving patient suffering.

2. ER/LA Opioids Are Appropriate for Certain Patients

In support of your requests to withdraw the approval of original OxyContin and Palladone until they can be reformulated to be of minimal abuse potential, you raise the issues of comparative safety and efficacy between ER/LA and immediate-release (IR) opioids. You state that ER/LA products "can be easily converted from sustained to one-time immediate release," and that "[i]ngestion of this immediate release form of the drug can be fatal or lead to opiate addiction" (Petition at 4). You also contend that the evidence shows "no difference" in safety and efficacy between IR and ER/LA opioid formulations (Petition at 4).

Improper use of any opioid can result in serious side effects, including overdose and death, and this risk is higher with ER/LA opioid analgesics—a fact that informed FDA's requirement that ER/LA opioids have a REMS.[34] FDA acknowledges that there are few rigorous scientific studies directly comparing the safety and effectiveness of ER/LA and IR opioids.[35] However, ER/LA opioids may offer important benefits for some patients. ER/LA formulations may achieve more stable blood drug levels, which may result in more consistent pain control than is achieved with short acting opioids, although the data are inconsistent.[36,37] Long-acting opioids offer the advantages of fewer doses per day and likely improve patient compliance. Additionally the reduced number of doses may allow patients to sleep through the night. However there is not sufficiently clear evidence from appropriately designed comparative trials to make a case for the use of one type of formulation over the other on the basis of clinical efficacy or safety. Ultimately, the decision whether to prescribe an IR or ER/LA opioid rests with the prescriber, and will depend on such factors as the patient's pain profile, the goals of pain therapy, and the patient's experiences with pain relief and functional improvement from treatment.

B. Request That the Indications for Use of OxyContin[38] and Palladone Be Narrowed

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OxyContin and Palladone relative to morphine are such that they are more dangerous than other opioids. *See* Van Rooyan Response at 6-7. However, you do not cite any evidence to support this claim.

[34] *See* section I, above.

[35] *See* Rauck, RL, 2009, What is the Case for Prescribing Long-Acting Opioids Over Short-Acting Opioids for Patients with Chronic Pain? A Critical Review, Pain Practice, 9(6), 468-479; Argoff, CL, and Silvershein, DI, 2009, A Comparison of Long-and Short-Acting Opioids for the Treatment of Chronic Noncancer Pain: Tailoring Therapy to Meet Patient Needs, Mayo Clinic Proc, 84(7): 602-612.

[36] Rauck, RL, 2009, What is the Case for Prescribing Long-Acting Opioids Over Short-Acting Opioids for Patients with Chronic Pain? A Critical Review, Pain Practice, 9(6), 468-479.

[37] Argoff, CL, Silvershein, DI, 2009, A Comparison of Long-and Short-Acting Opioids for the Treatment of Chronic Noncancer Pain: Tailoring Therapy to Meet Patient Needs, Mayo Clinic Proc, 84(7): 602-612.

[38] Your Petition asks that the indication be changed for original OxyContin, its generics, and Palladone. Approval of the NDA for original OxyContin has been withdrawn, and because of the determination that it was withdrawn for reasons of safety or effectiveness, there can be no generics to original OxyContin.