OCT 19 2017

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

RE: Docket No. FDA-2017-P-3064

Dear Mr. Thompson:

This letter responds to the petition for stay of action (PSA) you submitted, which was received by the Food and Drug Administration (FDA or Agency) on May 11, 2017. In the PSA, you request that FDA stay the effective date of the approval of Roxybond (oxycodone hydrochloride) (new drug application (NDA) 209777) with labeling claims pertaining to chronic use and abuse-deterrence until the Agency issues substantive written responses to the citizen petitions submitted by Pharmaceutical Manufacturing Research Services, Inc. (PMRS) dated February 19, 2016 (FDA-2016-P-0645) (2016 Petition)[1] and dated March 6, 2017 (FDA-2017-P-1359) (2017 Petition)[2] as well as to the issues raised in the PSA (PSA at 23).[3]

We have carefully considered the PSA. Among other issues, your PSA highlights the crisis of opioid addiction and abuse currently affecting the United States. While we welcome your engagement and that of other stakeholders on this critical public health subject, we do not agree that the requested stay would be in the public interest for reasons discussed below. In addition, while your 2016 Petition and 2017 Petition address matters of general relevance to opioid products, neither presents a basis for FDA to stay the approval of Roxybond while FDA considers such issues. For these reasons and the reasons stated below, the PSA is denied.

I. BACKGROUND

A. Roxybond

Roxybond is an immediate-release (IR) tablet indicated for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.

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[1] The 2016 Petition was received by the Agency on February 22, 2016. See Acknowledgement letter from FDA to PMRS dated February 22, 2016, available at https://www.regulations.gov/document?D=FDA-2016-P-0645-0002.

[2] The 2017 Petition was received by the Agency on March 6, 2017. See Acknowledgement letter from FDA to PMRS dated March 6, 2016, available at https://www.regulations.gov/document?D=FDA-2017-P-1359-0001.

[3] We note that, after submitting the PSA, you submitted a citizen petition (FDA-2017-P-4352), dated July 20, 2017, in which you request that FDA refrain from approving pending NDA 209653 with the proposed indication of "management of moderate-to-severe pain when a continuous around-the-clock analgesic is needed for an extended period of time" and refrain from approving all other pending or future applications for opioids indicated for chronic use. The July 20, 2017 petition is not within the scope of this response.

Roxybond is available in 5-milligram (mg), 15-mg, and 30-mg dosage strengths for oral administration every 4 to 6 hours as needed for pain.

Inspirion Delivery Services, LLC. (Inspirion) submitted NDA 209777 under Section 505(b)(2) of the Federal Food, Drug, and Cosmetic (FD&C) Act seeking approval of Roxybond. The Roxybond NDA was approved based in part on a demonstration of bioequivalence to the listed drug, Roxicodone (oxycodone hydrochloride, NDA 021011). To support the abuse-deterrent properties of Roxybond, Inspirion submitted in vitro, in vivo, and human abuse potential (HAP) studies.[4]

On April 20, 2017, FDA approved Roxybond, the first IR opioid with labeling describing abuse-deterrent properties. The labeling includes the following language regarding Roxybond's abuse-deterrent properties:

> The in vitro data demonstrate that ROXYBOND has physicochemical properties expected to make abuse via injection difficult. The data from the clinical study, along with support from in vitro data, also indicate that ROXYBOND has physicochemical properties that are expected to reduce abuse by the intranasal route of administration. However, abuse by the intranasal, oral, and intravenous route is still possible.
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> Additional data, including epidemiological data, when available, may provide further information on the impact of the current formulation of ROXYBOND on the abuse liability of the drug. Accordingly, this section may be updated in the future as appropriate.[5]

At present, there are no other FDA-approved IR opioid analgesics with labeling describing their abuse-deterrent properties.

B. Pending Petitions

In its 2016 Petition, PMRS requests that FDA apply "existing standards" for laboratory-based in vitro manipulation and extraction studies, including both small and large volume extractability/syringeability studies, for products seeking approval of labeling describing abuse-deterrent properties, and that the Agency remove Category 3 Clinical Abuse Potential Studies (HAP or liking studies) from the final guidance for industry entitled *Abuse-Deterrent Opioids – Evaluation and Labeling Guidance* (Abuse-Deterrent Guidance) (2016 Petition at 1, 3).[6] The 2016 Petition also requests that FDA "require post-marketing empirical proof through epidemiological or other scientifically rigorous studies that shows that opioid drug products with potential abuse deterrent properties do in fact result in a meaningful reduction in misuse, abuse,

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[4] HAP studies are also often referred to as "liking studies" or "abuse liability" studies and are referred to as Category 3 Clinical Abuse Potential studies in the guidance for industry, *Abuse-Deterrent Opioids – Evaluation and Labeling Guidance.*

[5] Approved labeling for Roxybond, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209777lbl.pdf.

[6] The Abuse Deterrent Guidance is available at https://www.fda.gov/downloads/Drugs/Guidances/UCM334743.pdf.

addiction, overdose and/or death before approving abuse deterrent labeling for opioid drug products and before permitting opioid drug products to be marketed as abuse deterrent" (2016 Petition at 1, 3, 4). The 2016 Petition further requests that, for any approved opioid products with abuse-deterrent labeling that do not meet these standards, FDA revise the labeling to remove the abuse-deterrent labeling claims (2016 Petition at 1, 4). Finally, the 2016 Petition requests that FDA revise the labeling for "Reformulated OxyContin" (oxycodone hydrochloride controlled release tablets (NDA 22272)) to remove the abuse-deterrent labeling claims, "revoke" the three-year exclusivity applicable to that product, and "restore" the NDA under which "Original OxyContin" (oxycodone hydrochloride controlled-release tablets (NDA 20-553)) was marketed (Petition at 4). In a letter dated August 25, 2016 and submitted to the docket for the 2016 Petition, PMRS provided additional information relating to the issues raised in that petition.[7]

In its 2017 Petition, PMRS requests that the Agency revoke approval of OxyContin's indication for "the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate" and all supporting chronic use labeling (2017 Petition at 1). The 2017 Petition further requests that we revoke approval of all extended-release opioids indicated for "the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate" (2017 Petition at 1). Finally, the 2017 Petition requests that FDA revoke approval of all IR opioid drug product labeling supporting use for the treatment of chronic pain (2017 Petition at 1). PMRS requests that labeling instead state that the indication is for "acute pain for a limited duration" (2017 Petition at 1).

As of the date of this letter, FDA has not granted or denied the 2016 Petition or the 2017 Petition.

II. DISCUSSION

You ask FDA to stay the effective date of approval for Roxybond until FDA issues a substantive response to the 2016 Petition, the 2017 Petition, and the PSA. Your request is denied.

FDA's regulation at 21 CFR 10.35(e) sets out the standard for review of a petition for stay of action as follows:

> The Commissioner may grant or deny a petition, in whole or in part; and may grant such other relief or take such other action as is warranted by the petition. The Commissioner may grant a stay in any proceeding if it is in the public interest and in the interest of justice. The Commissioner shall grant a stay in any proceeding if all of the following apply:
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> (1) The petitioner will otherwise suffer irreparable injury.
> (2) The petitioner's case is not frivolous and is being pursued in good faith.
> (3) The petitioner has demonstrated sound public policy grounds supporting

[7] See Amendment letter from PMRS to FDA dated August 25, 2016, available at https://www.regulations.gov/document?D=FDA-2016-P-0645-0013.

the stay.

(4) The delay resulting from the stay is not outweighed by public health or other public interests.

The Commissioner shall grant a stay if all four of these criteria apply. We need not address whether or not your request is frivolous and is being pursued in good faith (criteria 2) because we find that you have failed to meet the remaining three criteria, as explained below.

A. PMRS Has Not Demonstrated That It Will Suffer Irreparable Injury

You claim that you will suffer irreparable injury as a result of "the launch of ROXYBOND prior to FDA's consideration of the PMRS Petitions," for several reasons (PSA at 23). For example, you state that you will suffer irreparable injury because "Inspirion will begin marketing a less safe and effective drug with unsupported labeling claims, the harm from which will be attributed not only to it, but also to other opioid products labeled for abuse deterrence and chronic use, including other IRs" (PSA at 23). You state that, as a result, PMRS, "which has developed an [IR] abuse deterrent opioid for FDA approval, will be forced to suffer the detrimental effect that an improperly-studied product labeled with claims of abuse deterrence and with language suggestive of chronic use has on the market place in relation to other appropriately studied and labeled IR products formulated with 'abuse-deterrent' properties" (PSA at 23-24).

None of the allegations or information in the PSA demonstrate that PMRS will suffer irreparable injury absent a stay of Roxybond's approval. FDA does not agree that Roxybond is a "less safe and effective drug" or that its approved abuse-deterrent labeling is not sufficiently supported. FDA's rationale for approving Roxybond for the above-stated indication and with labeling describing the product's abuse-deterrent properties is set forth in the appropriate review documents.[8] In addition, prior to the Agency's approval of the Roxybond NDA, FDA's Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) and FDA's Drug Safety and Risk Management Advisory Committee (DSaRM) held a joint meeting to discuss the application.[9] While not binding on the Agency, the votes of the committee members also support FDA's conclusions regarding the product's abuse-deterrent properties.[10]

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[8] See reviews for Roxybond at https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process.

[9] See Briefing Information for the April 5, 2017 Joint meeting of the AADPAC and DSaRM available at https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/ucm550016.htm.

[10] In particular, on the question of whether Roxybond should be labeled as an abuse-deterrent product by the nasal route of abuse, the committees voted 19 to 1 in favor of labeling for abuse-deterrent properties by the nasal route. Summary Minutes of the AADPAC and DSaRM Joint Meeting April 5, 2017 at 5, available at https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM556517.pdf. On the question of whether Roxybond should be labeled as an abuse-deterrent product by the intravenous route of abuse, the committees voted 16 to 4 in favor of abuse-deterrent labeling. Id. at 6. Finally on the issue of whether Roxybond should be approved for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate, the committees voted 19 yes with 1 abstention. The committees stated that "this product shows an incremental advantage in abuse-deterrence and meets an important public health need." Id.

Moreover, as you note in the PSA, PMRS has developed and submitted an application to FDA for an IR opioid product that purports to have abuse-deterrent properties, but the application has not been approved (PSA at 26, footnote 115). Because it is not yet known whether or when the PMRS application will be approved, there can be no threat of irreparable injury to PMRS at this time.

B. PMRS Has Not Demonstrated Sound Public Policy Grounds Supporting a Stay

You state that there is "a strong public policy interest in FDA not approving the Inspirion NDA for the treatment of chronic pain and with abuse-deterrent labeling until the product is demonstrated to be safe and effective according to FDA's own regulations and recommendations" (PSA at 27). However, as explained above, FDA determined that Roxybond has been shown to be safe and effective in accordance with applicable standards, and nothing in your PSA causes the Agency to reconsider that decision.

In addition, the PSA refers to arguments raised in the 2016 Petition and 2017 Petition that you claim raise questions about the efficacy and safety of opioid drug products generally, and which you say therefore provide public policy grounds supporting a stay of the approval of Roxybond. For example, you point out that the 2017 Petition claimed that FDA has added "supporting labeling for chronic treatment" for IR opioids "despite the lack of substantial evidence" and that the 2016 Petition requested that FDA "remove HAP studies as a premarket requirement for abuse deterrent labeling" (PSA, at 27-28). Both the 2016 Petition and the 2017 Petition raise issues with potential applicability to many opioid drug products. Neither petition addresses the Roxybond NDA specifically, and neither petition presents a basis for FDA to stay the approval of Roxybond while the Agency considers such issues. If FDA's review of the information presented in the petitions were to result in changes to the Agency's approach to relevant products, the Agency generally would take appropriate regulatory action with respect to all affected applications.

In support of your argument relating to public policy grounds, you also claim that the Agency violated the Administrative Procedure Act by approving Roxybond before responding to the petitions (PSA at 27). In particular, you state that FDA's approval of Roxybond with "the same underlying significant substantive issues" raised in the 2016 Petition and the 2017 Petition is "arbitrary, capricious and not otherwise in accordance with the law" (PSA at 27). We understand your desire for a speedy resolution of your petitions, and we are working to respond to the 2016 Petition and 2017 Petition in a reasonable timeframe, given the existence of many competing priorities at FDA. The Agency intends do so in accordance with its applicable regulations.

In particular, FDA's regulations provide that the Commissioner "shall furnish a response to each petitioner within 180 days of receipt of the petition" and can make one of the following three choices:

(i) Approve the petition, in which case the Commissioner shall concurrently take appropriate action (e.g., publication of a Federal Register notice) implementing the approval;
(ii) Deny the petition; or

(iii) Provide a tentative response, indicating why the agency has been unable to reach a decision on the petition, e.g., because of the existence of other agency priorities, or a need for additional information. The tentative response may also indicate the likely ultimate agency response, and may specify when a final response may be furnished.

With respect to the 2016 Petition, we provided PMRS with an interim response on August 16, 2016.[11] With respect to the 2017 Petition, we provided PMRS with an interim response on August 31, 2017.[12] Accordingly, we have satisfied the requirements of the regulation.[13]

Moreover, we believe that the approval of opioid products with abuse-deterrent properties, such as Roxybond, supports public health. As noted above, Roxybond is the first IR opioid with labeling describing its abuse-deterrent properties. Based on currently available information, we believe that the approval of Roxybond is likely to be a step forward in the Agency's broader efforts to combat opioid abuse and misuse.

In sum, PMRS has not demonstrated sound public policy grounds that would support a stay of action.

C. Public Health and Other Public Health Interests Do Not Support a Stay

You state that it is in the public interest to stay the date of Roxybond's approval because, among other things, the introduction of abuse-deterrent opioids, like Roxybond, may provide "prescribers and patients with a false sense of security about the actual abuse potential of these products" (Petition at 29). The Agency has repeatedly stated that opioids with abuse-deterrent properties are not abuse-proof. For example, the Abuse-Deterrent Guidance states that:

> There are several important concepts about the state of the science of pre- and postmarket studies of abuse deterrence that should be considered as these are reflected in labeling. First, as stated earlier in the guidance, abuse-deterrent does not mean abuse-proof. Therefore, labeling should reflect a product's abuse-deterrent properties, as supported by the data, but should include a caveat that abuse is still possible.
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> Labeling language regarding abuse deterrence should describe the product's specific abuse-deterrent properties as well as the specific routes of abuse that the product has been developed to deter. For example, a formulation that limits an abuser's ability to crush a tablet and to extract the opioid can be described as limiting manipulation for the purpose of snorting or injection if the data support such a statement. For this characterization to be accurate and not misleading, however, appropriate caveats are likely to be necessary as described above. For example, a product's labeling should explain that the product's

[11] See CDER Interim Response Letter to PMRS dated August 16, 2016, available at https://www.regulations.gov/document?D=FDA-2016-P-0645-0012.

[12] See CDER Interim Response Letter to PMRS dated August 31, 2017, available at https://www.regulations.gov/document?D=FDA-2017-P-1359-0026.

[13] See *Biovail Corp. v. U.S. Food & Drug Admin.*, 448 F. Supp. 2d 154, 161-162 (D.D.C. 2006) (finding that FDA was not required to rule on the citizen petition by any particular date and it was appropriate to issue an interim response without substantively responding to the petition by the 180-day deadline).

> abuse-deterrent properties only make abuse more difficult, not impossible, and that these properties provide no deterrence against other potential forms of abuse.[14]

Consistent with the Abuse-Deterrent Guidance and the labeling for other products that have abuse-deterrent properties, Roxybond's labeling states that while Roxybond is expected to make abuse via injection and by the intranasal route of administration difficult, "abuse by the intranasal, oral, and intravenous route is still possible."[15] Because of this, and based on the relevant evidence currently available to the Agency, we do not agree that the risk you describe supports granting a stay of the Roxybond approval.

More generally, you suggest that a stay is warranted because the United States is currently experiencing an opioid epidemic (PSA, at 30). We agree that opioid addiction and the resulting overdoses and deaths have created a national crisis. Indeed, Commissioner Gottlieb has recently said that reducing the scope of the epidemic of opioid addiction is his highest immediate priority as Commissioner.[16] The Agency is taking several steps to address this public health concern, as discussed further below, and FDA does not believe that granting a stay of the Roxybond approval would advance efforts to combat the opioid crisis.

For example, the Agency is working to enhance prescriber and patient awareness of the safe use of opioids. On September 28, 2017, FDA notified holders of approved applications for IR opioid analgesics of the Agency's determination that a REMS is necessary for IR opioid analgesics to ensure that the benefits of these drugs continue to outweigh the risks, and the IR opioid analgesics that are intended to be used in the outpatient setting will be subject to the same REMS requirements as the extended-release (ER)/long-acting (LA) opioid analgesics.[17] The REMS will include revisions to the "FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics" (Blueprint), which requires that training in the form of accredited continuing education be made available to health care providers who prescribe IR and ER/LA opioid analgesics. The accredited continuing education must include all elements of the FDA Blueprint, which includes a basic outline and the core messages related to IR and ER/LA opioid analgesics. The revisions to the Blueprint include information on pain management, including the principles of acute and chronic pain management, non-pharmacologic treatments for pain, and pharmacologic treatments for pain (both non-opioid analgesic and opioid analgesic).

In addition, the Agency is undertaking a study to improve its understanding of prescriber beliefs

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[14] Abuse-Deterrent Guidance at 22.

[15] Approved labeling for Roxybond, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209777lbl.pdf.

[16] See Scott Gottlieb, M.D., Commissioner of Food and Drugs, Remarks Delivered Before FDA's Scientific Meeting on Opioids (Jul. 10, 2017), available at https://www.fda.gov/newsevents/speeches/ucm566189.htm.

[17] See Risk Evaluation and Mitigation Strategy (REMS) for Opioid Analgesics, available at https://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm163647.htm.

relating to use of opioid products with abuse-deterrent properties.[18] The Agency is evaluating currently-used nomenclature for such products, including by surveying doctors to better understand how they perceive these terms and to assess the clinical understanding that has developed around products with labeling for abuse-deterrent properties. Further, FDA is continuously monitoring the safety of approved opioid products based on post-market information, including through a focus on improving post-market data collection in this area.

As the above illustrates, the Agency recognizes the critical importance of the opioid crisis, which the Commissioner has called a "public health tragedy of enormous proportions."[19] We do not agree, though, that granting the stay you request would be an appropriate response to this crisis, or that it would be in the public interest to do so. Indeed, we believe that having Roxybond available as an option for prescribers is in the public interest. Roxybond is the first IR opioid with abuse-deterrent labeling claims approved by FDA. Based on currently available information, we believe that the approval of Roxybond is a step forward in the Agency's broader efforts to combat opioid abuse and misuse.

You also note that, in addition to the PSA and the citizen petitions you have submitted to FDA, PMRS has participated in FDA Advisory Committee meetings and public workshops related to opioid products (PSA at 3). FDA welcomes this engagement and recognizes the valuable perspective that PMRS and other stakeholders continue to provide on matters relating to the opioid crisis.

FDA also acknowledges your request that, even if we determine that your PSA does not satisfy all of the criteria for a "mandatory" stay, the Agency nonetheless should grant a stay under its discretionary authority (PSA at 23, footnote 101). Under 21 CFR 10.35(e), FDA may grant a stay in any proceeding if it is in the public interest and in the interest of justice. As explained above, while the Agency agrees that the opioid crisis is a public health emergency of critical importance, we do not agree that the action you request would mitigate the crisis or otherwise be in the public interest.

III. CONCLUSION

For the reasons described above, the requests set forth in the PSA are denied.

Sincerely,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

[18] See Scott Gottlieb, M.D., Commissioner of Food and Drugs, Remarks Delivered Before FDA's Scientific Meeting on Opioids (Jul. 10, 2017), available at https://www.fda.gov/newsevents/speeches/ucm566189.htm.

[19] Id.