PHARMACEUTICAL MANUFACTURING RESEARCH SERVICES, INC.

May 11, 2017

Via Electronic Submission

Dockets Management Branch, HFA-305
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: Docket No. FDA-2016-P-0645
Docket No. FDA-2017-P-1359

PETITION FOR STAY OF ACTION

Dear Sir or Madam:

The undersigned, on behalf of Pharmaceutical Manufacturing Research Services, Inc. ("PMRS"), respectfully submits this petition pursuant to 21 C.F.R. § 10.35 and the federal Food, Drug and Cosmetic Act, among other provisions of law, to request that the Commissioner of Food and Drugs ("the Commissioner") stay the effective date of the approval[1] of New Drug Application 209777 for ROXYBOND (oxycodone hydrochloride) tablets, submitted by Inspirion Delivery Sciences, LLC ("Inspirion") pursuant to Section 505(b)(2) of the federal Food, Drug, and Cosmetic Act (FDCA) (the "Inspirion NDA" or "ROXYBOND").

Specifically, PMRS requests that the Commissioner stay the effective date of the approval of NDA 209777 with labeling claims pertaining to (1) chronic use; and (2) abuse deterrence until the U.S. Food and Drug Administration ("FDA") issues a substantive written response to the citizen petitions submitted by PMRS on February 19, 2016 (Docket No. FDA-2016-P-0645) (the "February 2016 Petition")[2] and March 6, 2017 (Docket No. FDA-2017-P-1359) (the "March

[1] The approval decision for ROXYBOND was not publicly announced by Inspirion until April 26, 2017. Press Release, Inspirion Delivery Sciences, LLC, Inspirion Delivery Sciences Receives FDA Approval for RoxyBond™ (oxycodone hydrochloride) tablets CII, the First and Only Immediate Release Opioid Analgesic with Abuse-Deterrent Label Claims (Apr. 26, 2017), http://www.prnewswire.com/news-releases/inspirion-delivery-sciences-receives-fda-approval-for-roxybond-oxycodone-hydrochloride-tablets-cii-the-first-and-only-immediate-release-opioid-analgesic-with-abuse-deterrent-label-claims-300445964 html (last visited May 11, 2017). However, the official approval letter from FDA is dated April 20, 2017. Letter from Sharon Hertz, M.D., Director, Division of Anesthesia, Analgesia, and Addiction Products, CDER, to Inspirion Delivery Sciences, LLC, Approval Letter for NDA 209777 (Apr. 20, 2017), https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2017/209777Orig1s000ltr.pdf (last visited May 11, 2017). In other words, it appears that FDA granted final approval of the Inspirion NDA a mere 10 business days after the conclusion of the Advisory Committee meeting. At the time of FDA's approval, PMRS was preparing a petition requesting that FDA refrain from approving the Inspirion NDA due to the significant issues with the data and other information presented at the April 5th Advisory Committee meeting for the Inspirion NDA, including related issues raised in the PMRS Petitions.

[2] As supplemented by the August 25, 2016 PMRS supplemental correspondence.

2017 Petition") (collectively, the "PMRS Petitions") and to the issues raised in this petition, including the specific deficiencies in the Inspirion data and information as discussed herein.[3]

By way of a brief summary of the pending PMRS Petitions, the February 2016 Petition submitted by PMRS requested, in part, that FDA take the following actions:

> (i) apply the existing standards for laboratory-based in vitro manipulation and extraction studies, including both small and large volume extraction, before permitting opioid drug products with potentially abuse-deterrent properties to be approved;
>
> (ii) Remove Category 3 human abuse-deterrent (liking) studies from the FDA Guidance, "Abuse-Deterrent Opioids Evaluation and Labeling Guidance for Industry" (April 2015) (the "Guidance"), and as a requirement for approval of drug products with potentially abuse deterrent properties as inherently flawed, subjective, and highly prone to manipulation;
>
> (iii) 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, 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.[4]

The March 2017 Petition submitted by PMRS requested, in part, the revocation of all immediate-release (IR) opioid drug product labeling "supporting use for the treatment of chronic pain."[5] PMRS further requested that all IR opioid drug product labeling state that the indication is for "acute pain for a limited duration."[6]

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[3] As this instant petition raises other substantive issues concerning the Inspirion NDA in addition to those issues raised previously in the PMRS Petitions, FDA may wish to also create a separate docket for this petition in addition to submitting it to the above-captioned dockets for the pending PMRS Petitions.

[4] *See* PMRS, Citizen Petition, Docket No. FDA-2016-P-0645, at 3-4 (Feb. 19, 2016) (emphasis added) [hereinafter "February 2016 Petition"]. PMRS also requested that all opioid drug products currently labeled with abuse-deterrent claims be required to meet all three of the requirements specified above or have their abuse-deterrent labeling removed within a reasonable period of time not to exceed six months. In addition, the February 2016 Petition included a request for actions pertaining to OXYCONTIN specifically. *Id.* at 4. The OXYCONTIN-specific requests are not addressed herein.

[5] PMRS, Citizen Petition, Docket No. FDA-2017-P-1359, at 1 (Mar. 6, 2017) [hereinafter "March 2017 Petition"]. While this action was directed at withdrawing currently approved opioid products with labeling that supports chronic use, PMRS was not aware of any pending NDAs for such use. In any case, the substantive issues have equal and obvious prospective scientific and clinical application, as do the issues raised in the February 2016 Petition.

In addition, the March 2017 Petition also included a request for action with respect to (1) the OXYCONTIN labeled indication specifically, and (2) the labeled indication for all other extended-release (ER) opioids. *Id.*

[6] *Id.*

FDA has approved the Inspirion NDA without having provided a substantive response to the PMRS Petitions[7], yet, as discussed in detail herein, that approval is contrary to several of the actions requested and underlying issues raised in the pending PMRS Petitions. In addition, and as also discussed herein, there are significant flaws in the study methodology, data and information submitted by Inspirion, and ostensibly relied upon by FDA, in approving the Inspirion NDA. PMRS, therefore, respectfully requests that FDA stay the effective date of the approval of the Inspirion NDA 209777 with labeled claims for chronic use and abuse deterrence.

PMRS further requests that FDA provide a substantive response to this Petition for Stay of Action by June 12, 2017. The underlying issues raised in the PMRS Petitions have been before FDA for some time, and were raised by PMRS in the form of a Citizen Petition as long as 15 months ago. Time is of the essence. And not just for PMRS. The issues raised but not yet answered are of a pressing public health concern as they are germane to the U.S. opioid abuse epidemic that is raging in the U.S.[8]

A. DECISION INVOLVED

In this section, PMRS discusses in detail the decision that is the subject of this Petition for Stay—FDA's approval of the Inspirion NDA—and why the effective date of that approval should be stayed.

On April 20, 2017, FDA approved the Inspirion NDA without providing PMRS with any substantive response to the issues that PMRS has raised time and time again, including in the February 2016 and March 2017 Citizen Petitions.

Indeed, PMRS has engaged directly with FDA nearly at every turn, publicly advocating for the dire public-health need for the Agency to reassess its approach to approving opioid products. PMRS has engaged not only through the submission of the Citizen Petitions referenced above, but also in numerous FDA Advisory Committee meetings and public workshops.[9] Notably, however, to date, PMRS has received no substantive response, no substantive information, thus no substantive rationale for FDA's continuing with a seemingly status quo approach.

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[7] To date, PMRS has received only a one-page procedural "interim response" to the February 2016 Petition. *See* Letter from Carol J. Bennett, Deputy Director, Office of Regulatory Policy, CDER, to Edwin R. Thompson, President, Pharmaceutical Manufacturing Research Services, Inc., Docket No. FDA-2016-P-0645, (Aug. 16, 2016).

[8] *See* Laurie McGinley, *FDA nominee says nation's opioid crisis is as serious as Ebola, Zika threats*, WASH. POST (Apr. 5, 2017), https://www.washingtonpost.com/news/to-your-health/wp/2017/04/05/fda-nominee-says-nations-opioid-crisis-is-as-serious-as-ebola-zika-threats/?utm_term=.9c3adc84c3a2 (last visited May 11, 2017) (noting that "[d]uring his confirmation hearing before the Health, Education, Labor and Pensions Committee, [recently confirmed FDA Commissioner] Gottlieb described the FDA as 'complicit, even if unwittingly,' in helping to fuel the opioid epidemic.").

[9] *See generally* PMRS's comments at the advisory committee meetings pertaining to VANTRELA ER (Jun. 7, 2016), TROXYCA ER (Jun. 8, 2016), ARYMO ER (Aug. 4, 2016), the use of opioids in pediatric patients (Sep. 16, 2016), OPANA ER (Mar. 14, 2017), and ROXYBOND (Apr. 5, 2017) as well as the public meeting on premarket evaluation of abuse-deterrent properties (Nov. 1, 2016).

In the face of that ongoing silence, and contrary to the issues raised in the PMRS Petitions, FDA has now approved yet another opioid product with so-called abuse-deterrent labeling—an immediate-release formulation, the Inspirion NDA—based on reliance on flawed study methodology, data, and other information provided. In addition, FDA has approved the Inspirion NDA with labeling that supports the broad use of yet another opioid product for chronic pain—a use without clinical merit except in very limited circumstances.[10] Meanwhile, the opioid abuse epidemic continues to rage and the number of overdose related deaths continues to climb.

1. FDA's Approval of the Inspirion NDA Is Contrary to the Pending PMRS Petitions

As noted above, PMRS currently has two Citizen Petitions pending before FDA which request that the Agency take certain specific actions with respect to opioid drug products. Without providing PMRS with a substantive response to those Petitions, FDA has continued to approve new opioid drug products contrary to the issues raised in those Petitions.[11]

Discussed in detail below are the reasons that the effective date of the approval of the Inspirion NDA should be stayed, including how such approval is contrary to each of the applicable requests in the PMRS Petitions. In addition, also discussed below are additional grounds on which the approval of the Inspirion NDA is inappropriate and should be stayed.

a. FDA Should Not Approve Opioid Drug Products with Labeling Supporting the Use for the Treatment of Chronic Pain in the General Population

FDA has repeatedly approved opioid drug products for the treatment of chronic pain despite a lack of substantial evidence supporting the efficacy of these products in the chronic-use setting. Thus, in its March 2017 Petition, PMRS requested that FDA revoke approval for all opioid products that support the treatment of chronic pain. In that same petition, and with additional specificity to further mitigate the significant risk of addiction posed by use for chronic pain, PMRS requested that the labeling of IR opioid products state that the product is indicated for

[10] Consistent with the CDC's *Guideline for Prescribing Opioids for Chronic Pain*, PMRS generally believes that such circumstances should be limited to the treatment of patients undergoing active cancer treatment, palliative care, or end-of-life care. *See* CDC, *Guideline for Prescribing Opioids for Chronic Pain*, at 3 (2016), https://www.cdc.gov/mmwr/volumes/65/rr/pdfs/rr6501e1.pdf (last visited May 11, 2017) ("The guideline is not intended for patients undergoing active cancer treatment, palliative care, or end-of-life care because of the unique therapeutic goals, ethical considerations, opportunities for medical supervision, and balance of risks and benefits with opioid therapy in such care.").

[11] Since PMRS filed its February 2016 Petition, FDA has approved the following opioid drug products with abuse-deterrent labeling: XTAMPZA ER, VANTRELA ER, TROXYCA ER, ARYMO ER, and ROXYBOND.

"acute pain for a limited duration."[12] Before submitting the March 2017 Petition, PMRS had previously raised this issue in other advisory committee meetings.[13]

In spite of this pending Petition, FDA proceeded to approve the Inspirion NDA with labeling supporting the use of the product for the treatment of chronic pain. The labeled indication is worded broadly, stating that it is "for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate."[14] Section 2.2 of the label further states, "[f]or control of chronic pain, administer ROXYBOND on a regularly scheduled basis, at the lowest dosage level to achieve adequate analgesia."[15]

The labeling approved with the Inspirion NDA is also at odds with public statements made by high-ranking officials at both the CDC and the FDA. For example, when discussing the release of its new *Guidelines for Prescribing Opioids for Chronic Pain*, the CDC noted that: "Most placebo-controlled, randomized trials of opioids have lasted 6 weeks or less, and we are aware of no study that has compared opioid therapy with other treatments in terms of long-term (more than 1 year) outcomes related to pain, function, or quality of life. The few randomized trials to evaluate opioid efficacy for longer than 6 weeks had consistently poor results."[16] The CDC went on to observe that "[t]he science of opioids for chronic pain is clear: for the vast majority of patients, the known, serious, and too-often-fatal risks far outweigh the unproven and transient benefits."[17] Accordingly, the CDC's current position is that the "evidence reviews forming the basis of this guideline clearly illustrate that there is much yet to be learned about the effectiveness, safety, and economic efficiency of long-term opioid therapy."[18]

FDA has stated its intent to support the CDC's *Guidelines for Prescribing Opioids for Chronic Pain*.[19] Consistent with the CDC's remarks, the FDA has also noted that "[d]espite ongoing efforts, the evidence base to guide the use of opioid medications, particularly in the setting of long-term use, is substantially lacking."[20] The FDA has further commented that: "Unfortunately,

[12] March 2017 Petition, at 1.
[13] PMRS raised this issue in the public advisory committee meetings that discussed TROXYCA ER (Jun. 8, 2016), ARYMO ER (Aug. 4, 2016), and the safety and efficacy of prescription opioids for pediatric patients (Sep. 16, 2016). *See, e.g.*, ARYMO Advisory Committee Meeting, at 147 (noting that "there is no scientific evidence showing the efficacy of long-term opioid treatment"); Pediatric Opioids Advisory Committee Meeting, at 47 (noting that "there is no substantial evidence of efficacy for opioids in chronic treatment of pain").
[14] ROXYBOND Highlights of Prescribing Information (Rev.: Apr. 20, 2017), Dosage and Administration, https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209777lbl.pdf (last visited May 11, 2017).
[15] *Id.*
[16] March 2017 Petition, at 3 (quoting Thomas R. Frieden & Debra Houry, *Reducing the Risks of Relief — The CDC Opioid-Prescribing Guideline*, 374 New Eng. J. Med. 1501, 1501 (2016)).
[17] *Id.* at 3 (quoting Thomas R. Frieden & Debra Houry, *Reducing the Risks of Relief — The CDC Opioid-Prescribing Guideline*, 374 New Eng. J. Med. 1503 (2016)).
[18] *Id.* (quoting CDC, *Guideline for Prescribing Opioids for Chronic Pain* 34 (Mar. 18, 2016), https://www.cdc.gov/mmwr/volumes/65/rr/pdfs/rr6501e1.pdf (last visited May 11, 2017)).
[19] Robert M. Califf et al., *A Proactive Response to Prescription Opioid Abuse*, 374 New Eng. J. Med. 1480, 1483 (2016) [hereinafter "A Proactive Response to Prescription Opioid Abuse"].
[20] *Id.* at 1481.

the field of chronic pain treatment is strikingly deficient in such evidence. A key lesson learned during the development of the CDC guideline is that there is very little research on the long-term benefits of opioids for treating chronic pain."[21]

As the approval of the Inspirion NDA with this labeling contravenes the substantive underlying issues raised previously by PMRS in its March 2017 Petition, and further perpetuates the risk of opioid abuse, FDA should grant this stay of approval and provide PMRS with a substantive response to its Petitions.

b. FDA Should Adhere to the Agency's Existing Recommendations for Laboratory-based In Vitro Manipulation and Extraction Studies When Evaluating Opioid Drug Products With Potentially Abuse-deterrent Properties

In its February 2016 Petition, PMRS requested that FDA "[a]pply the existing standards for laboratory-based in vitro manipulation and extraction studies, including both *small* and *large* volume extraction, before permitting opioid drug products with potentially abuse deterrent properties to be approved."[22] FDA's approval of the Inspirion NDA is contrary to that very request. In approving the Inspirion NDA, FDA effectively rejected the requests made in the February 2016 Petition but without providing PMRS with any substantive response, including the rationale for any such rejection.

As FDA states in the guidance on evaluating abuse-deterrent opioids, laboratory-based in vitro physical manipulation and chemical extraction studies (Category 1 studies) are "critical to the understanding of product characteristics and performance."[23] The goal of Category 1 studies is to evaluate the potentially abuse-deterrent properties of a formulation by manipulating the product to the point of defeat.[24] To accomplish this goal, FDA has recommended that sponsors "assess various simple and sophisticated mechanical and chemical ways a drug could be manipulated."[25] This assessment consists of physical manipulation studies to determine whether the particle size of the product can be reduced and chemical extraction studies (small and large

[21] *Id.* at 1484.
[22] February 2016 Petition, at 3 (emphasis in original). In the February 2016 Petition, and in support of that general premise, PMRS selected an extended-release (ER) opioid drug product—Reformulated OXYCONTIN—as a specific case study to illustrate this general issue. However, the same concerns raised by PMRS in the February 2016 Petition apply with equal force to all opioid products—including IR products—as indicated by PMRS' remarks at the ROXYBOND advisory committee meeting. *See generally* Edwin R. Thompson, PMRS, Prepared Remarks at the Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM) (Apr. 5, 2017) (official transcript not yet available), https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM556517.pdf (last visited May 11, 2017).
[23] FDA, *Guidance for Industry: Abuse-Deterrent Opioids—Evaluation and Labeling*, at 6 (Apr. 2015), https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm334743.pdf (last visited May 11, 2017) [hereinafter "AD Opioid Evaluation and Labeling Guidance"].
[24] *Id.* at 6.
[25] *Id.*

volume) to determine whether the opioid can be selectively extracted from the intact and manipulated product.[26] As discussed in detail below, the in vitro studies for the Inspirion NDA neither complied with these recommendations nor offered a scientifically justified alternative approach.

(1) The Design of the Particle Size Manipulation Study Was Arbitrary

Opioid drug products may be physically manipulated by abusers in an attempt to prepare the formulation for abuse by alternative routes of administration, such as by intranasal or intravenous use. According to data presented in the Inspirion briefing information, 36% of IR oxycodone users reported abuse by the intranasal route making this the second most common route of administration following oral abuse.[27] For products with potential for abuse by the nasal route, FDA recommends that "the particle size distribution following attempted manipulation by various methods should be established, and the method that provides the *smallest* particle size should be used in subsequent studies."[28] FDA also recommends that "[p]articular attention should be given to particle size distribution following each mode of physical manipulation because particle size may influence the rate of opioid extraction from manipulated product."[29]

In a related FDA guidance on evaluating generic abuse-deterrent opioid products, FDA stated that "[t]he measure considered meaningful for evaluation of reduced availability [of insufflated opioid drug product] is the % mass of fine particles **(<500 µm)** available for insufflation."[30] The studies conducted to support the Inspirion NDA failed to focus its subsequent studies on the manipulation producing the greatest amount of particles below 500 µm.

Inspirion summarized the following results for the abuse deterrence Category 1 study ARS-122-06 at the April 5, 2017 FDA Advisory Committee meeting:

- ROXYBOND demonstrated resistance to common types of physical manipulation. An electric tool was the only tool able to produce small homogenous particles of ROXYBOND amenable for snorting. In comparison, ROXICODONE was easily manipulated into a fine powder in seconds with a mechanical tool.[31]

[26] *Id.*
[27] Inspirion, Briefing Information, Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM), at 16 (Apr. 5, 2017), https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/ucm550016 htm (last visited May 11, 2017) [hereinafter "Inspirion Briefing Information"].
[28] AD Opioid Evaluation and Labeling Guidance, at 7.
[29] *Id.* at 6.
[30] FDA, *Draft Guidance for Industry: General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products*, at 26 (Mar. 2016) (emphasis added), https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm492172.pdf (last visited May 11, 2017) [hereinafter "Generic AD Opioid Draft Guidance"].
[31] Inspirion Briefing Information, at 11.

- Pre-treatment of ROXYBOND by extreme changes to temperature did not significantly increase the effectiveness of particle size reduction with household tools.[32]

Notably, in reaching these conclusions, Inspirion arbitrarily set a target particle size, specifying "small particles (<2000 microns) amenable for insufflation."[33] Under this metric, Tool G was the most effective, achieving 92% of particles less than 2000 microns.[34] FDA's chemistry review of this study acknowledged the sponsor's selection of Tool G "as the only tool to produce a fine, relatively homogenous powder sufficient for intranasal insufflation."[35] Furthermore, particles produced by Tool G were subsequently used in Category 1 extraction studies as well as a Category 2/3 human abuse potential ("HAP") study with pharmacokinetic evaluation.[36]

Herein lies the rub. FDA's specification for meaningful evaluation of insufflation deterrence is the percent mass of fine particles available at less than 500 microns,[37] not the 2000 micron threshold defined by the sponsor. FDA's 500 micron specification is viewed as scientifically reasonable and thus, a commonly accepted particle size for an insufflation study. Inspirion's metric of <2000 microns has no basis or precedent in current FDA guidance, nor has the sponsor provided adequate scientific justification for the alternative approach. Attempts to insufflate large particles, such as those produced by Tool G, will cause the particles to bypass the nasal membranes and instead enter the gastrointestinal tract, significantly impacting the results of the study.[38]

Review of the study results (see Figure 1) in the context of the particle sizes available below 2000 microns rather than below 500 microns, indicates that the wrong tool was selected for the particle size manipulations performed in subsequent studies.

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[32] *Id.*
[33] *Id.* at 27.
[34] *Id.* at 28.
[35] FDA, Briefing Information, Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM), at 97 (Apr. 5, 2017), https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/ucm550016 htm (last visited May 11, 2017) [hereinafter FDA Briefing Information].
[36] Inspirion Briefing Information, at 11-12.
[37] Generic AD Opioid Guidance, at 26.
[38] *See, e.g.*, Transcript, Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM), at 163-164 (May 5, 2016), https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM507562.pdf (last visited May 11, 2017).

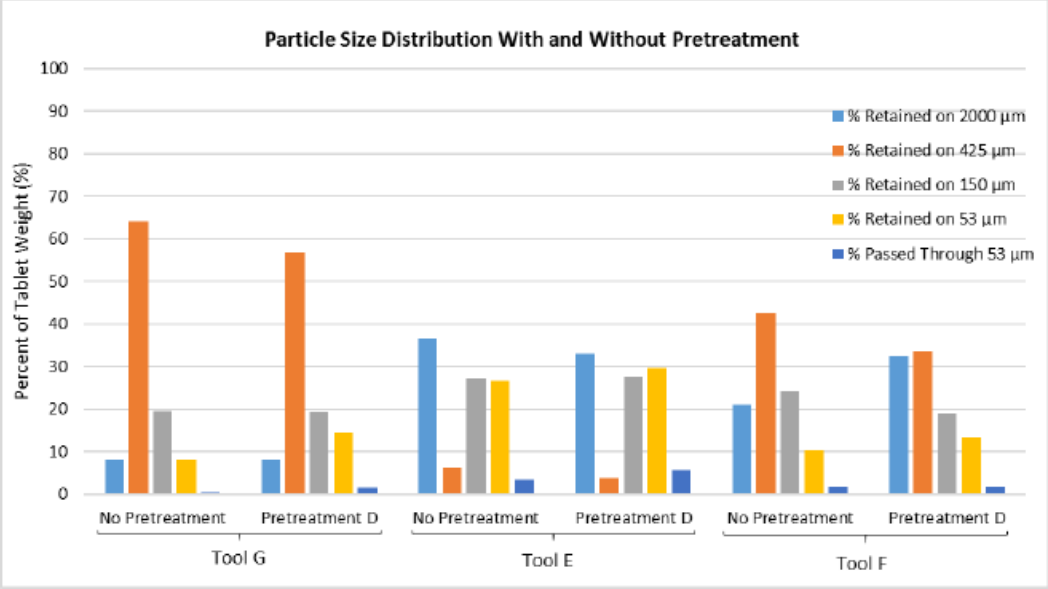

Figure 1 – Sponsor's particle size reduction study[39]

Again, the sponsor's study was predicated on the assumption that particles below 2000 microns were acceptable for evaluating insufflation. It is only by use of this invalid and unjustified metric that Tool G can be claimed to be an appropriate choice (see Figure 2). This is because 92% of the particles passed through the 2000 micron screen and were considered viable for the study.[40]

[39] FDA Briefing Information (Addendum), at 1.
[40] Inspirion Briefing Information, at 28.

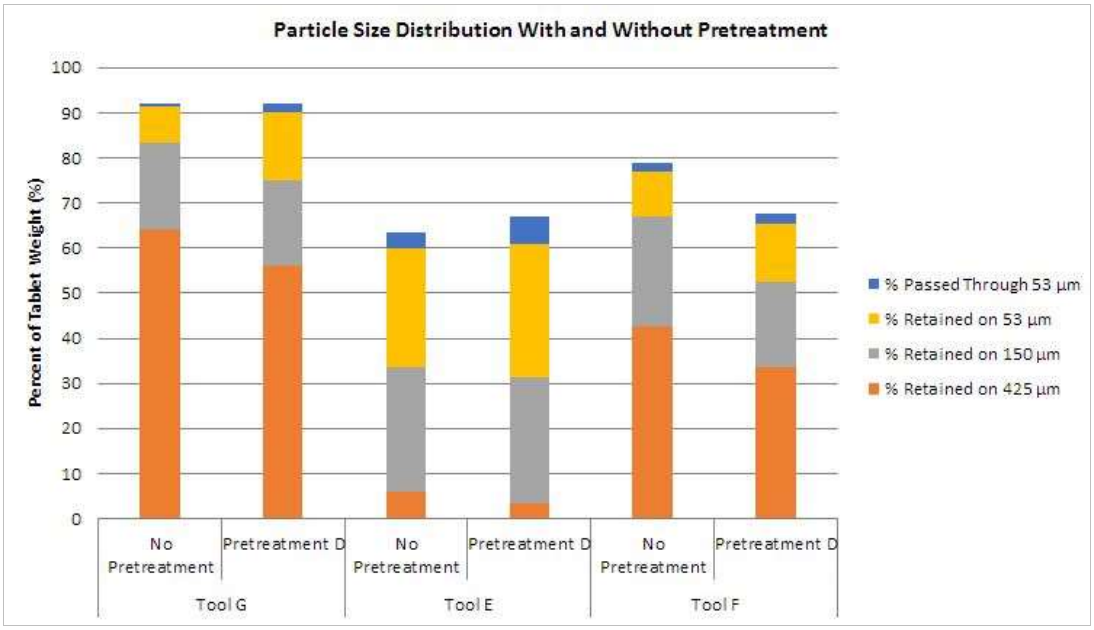

Figure 2 – Alternative visualization of sponsor's particle size data (excluding >2000 µm)

The use of a 2000 micron screen and a 425 micron screen in this study are inadequate in experimentally determining what percentage of particles would be below 500 microns and therefore available for insufflation. As seen in Figure 1, Tool G retains a majority of the particles on the 425 micron screen, but the range of particles in this category is between 425 microns and 2000 microns, exceeding the scientifically valid and commonly accepted specification of less than 500 microns[41] that also has been recognized by FDA. Given the wide range of particles in this category, it is not possible to draw accurate and sound conclusions from this data. During discussion before the ROXYBOND FDA Advisory Committee, these particles as used in the subsequent HAP study were discussed as including large granules (see Figure 3)[42]—seemingly inappropriate for the purpose of assessing insufflation—and certainly not the "fine, relatively homogeneous powder" referenced in the FDA chemistry review[43] and claimed by the sponsor.[44]

[41] Generic AD Opioid Guidance, at 26.
[42] Inspirion, Presentation, Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM), at 75 (Apr. 5, 2017), https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/ucm551776 htm (last visited May 11, 2017) [hereinafter "Inspirion Presentation"].
[43] FDA Briefing Information, at 97.
[44] Inspirion Briefing Information, at 11.

Figure 3 - Sponsor's FDA Advisory Committee "Tool G" particle size presentation slide[45]

The FDA chemistry review further stated, "Tools D and E can also be used to particle size reduce the Oxycodone ARIR [ROXYBOND] tablets, but not to the extent of mostly an insufflatable powder."[46] Yet, the sponsor's own data in Figure 1 demonstrates that a majority of the tablet can be manipulated to powder below the critical threshold of 500 microns by using Tool E. Using Tool G results in the opposite outcome. An alternative visualization of this distribution can be seen in Figure 4.

[45] Inspirion Presentation, at 75.
[46] FDA Briefing Information, at 97.

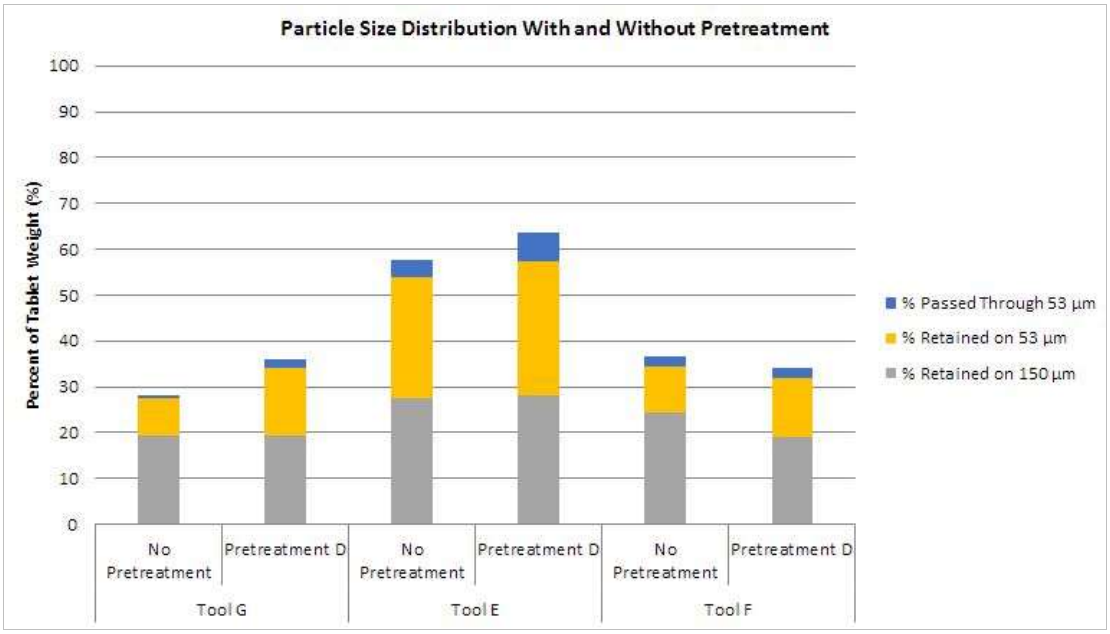

Figure 4 – Alternative visualization of sponsor particle size data (excluding >2000 µm and >425 µm)

A review of this distribution makes clear that the appropriate choice to evaluate insufflation deterrence with fine particles available at less than 500 microns is Tool E with Pretreatment D, which resulted in over 60% of the particles being available for insufflation at less than 500 microns. The sponsor's conclusion of Tool G with no pretreatment is not reasonable; indeed, it is the tool that least meets the Guidance criteria for manipulating ROXYBOND into fine particles suitable for insufflation, on the basis of producing less than 30% of particles available at less than 500 microns.

Inspirion's conclusion based on the particle size manipulation in study ARS-122-06 is flawed and misleading, as the experimental approach was not supported by Guidance nor has the sponsor demonstrated this to be an acceptable alternative approach to the Guidance. Reliance on this flawed and misleading conclusion by the sponsor in its further evaluations of ROXYBOND's abuse-deterrent properties causes subsequent studies, including the pivotal HAP study O-ARIR-002, to be invalid.

(2) The ROXYBOND Extraction Studies are Incomplete

As previously noted, FDA recommends that sponsors assess both simple and sophisticated chemical ways an opioid product could be manipulated, with the goal of these studies being to manipulate the product to the point at which its abuse-deterrent properties are defeated.[47] FDA recommends that chemical extraction studies be designed to determine whether any of the formulation components—e.g., the opioid—might be differentially extracted, allowing an abuser

[47] AD Opioid Evaluation and Labeling Guidance, at 6.

to bypass the product's abuse-deterrent properties.[48] Further, FDA recommends that sponsors determine whether free-base opioid can be precipitated from solution by pH adjustment—a relatively sophisticated manipulation that would allow recovery of solid opioid for subsequent abuse.[49] Inspirion should not have been approved because it failed to fully investigate the known ways in which opioid might be extracted from intact ROXYBOND tablets and then recovered in solid form from this solution.

As demonstrated in Figure 5 and documented in the FDA chemistry review, efficient extraction of ROXYBOND can be performed "with greater than 80% extracted by 15 minutes from the intact tablets."[50]

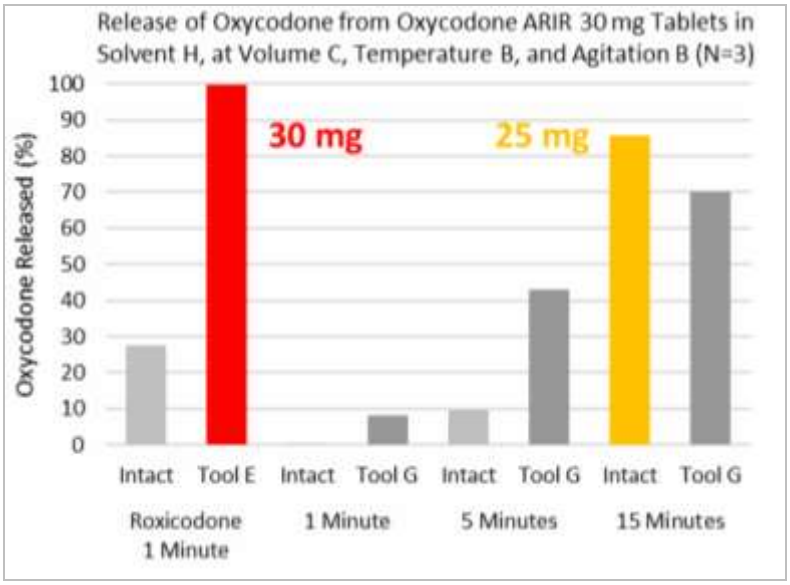

Figure 5 – Alternative visualization of sponsor large volume extraction data[51]

Although Inspirion evaluated other solvents and extraction methods, the worst-case scenario in which the most drug product is extracted in the shortest amount of time must be considered as the optimal method of extraction. If Inspirion had recovered oxycodone from extracted ROXYBOND tablets, and then tested the resulting solid particles against the reference product, the sponsor would likely have seen little to no difference in the other premarket studies—including the HAP study—between the 25 mg of oxycodone present in the extract and the 30 mg available in the reference product.

(3) The ROXYBOND Syringeability Studies Are Incomplete

[48] *Id.* at 6-7.
[49] *Id.* at 7.
[50] FDA Briefing Information, at 99.
[51] FDA Briefing Information (Addendum), at 3.

FDA's Guidance provides illustrative examples of the kinds of outcomes that in vitro studies should evaluate based on particular routes of administration.[52] Data presented in the Inspirion NDA briefing information suggests that 17% of IR oxycodone users reported abuse by the intravenous (IV) route.[53] For products with potential for abuse by injection, FDA's Guidance specifically recommends that the sponsor assess the: "Quantity of the opioid extracted from the product following the various methods attempted that could be used for injection by intravenous or subcutaneous routes and a description of any barriers resulting from attempts at dissolution for drawing the drug into a syringe."[54] Because Inspirion did not fully investigate whether opioid extracted from ROXYBOND using the known method discussed in Section A.1.b(2), *supra*, could be used for intravenous injection, the Inspirion NDA should not have been approved.

Inspirion's syringeability and small volume extraction test (ARS-122-08) reached the conclusion that "manipulated [ROXYBOND] tablets resisted extraction in addition to forming a viscous solution that was difficult to syringe."[55] This has been a common, yet false, conclusion in studies of many FDA-approved opioids which claim abuse-deterrent properties.[56]

Inspirion's own data demonstrate that oxycodone can be efficiently extracted (greater than 80%) from intact ROXYBOND tablets using Solvent H in 15 minutes.[57] However, the syringeability study concluded manipulated tablets resisted extraction after reviewing only small-volume extraction data which still showed the drug releases 66% in 30 minutes.[58] ROXYBOND must be evaluated on the merits of the extraction method (which the sponsor demonstrated) that produces the highest quantity of drug in the shortest period of time. It is only this extraction method which extracts the most drug in the shortest period of time that can be used to evaluate the abuse-deterrent properties of the drug.

Furthermore, the belief that gelling properties can be relied upon for abuse deterrence is false and misleading. The sponsor claims that the product is difficult to syringe when ground and made into a gel. Information concerning the ease with which polymer-based formulations can be manipulated by unskilled individuals using household items has previously been communicated to the FDA.[59] Although gelling can take place as demonstrated by the sponsor,[60] it does not impede the extraction of active ingredient from the drug product. The available data show that the intact tablet releases the API faster than the manipulated form. Thus, [redacted] In the OXYCONTIN case study (using PEO as a gelling agent), the extracted material does not contain

[52] AD Opioid Evaluation and Labeling Guidance, at 7-8.
[53] Inspirion Briefing Information, at 16.
[54] AD Opioid Evaluation and Labeling Guidance, at 8.
[55] Inspirion Briefing Information, at 36.
[56] *See* FDA Briefing Information, at 63 (OXYCONTIN), 72 (HYSINGLA ER), 77 (MORPHABOND), 79 (XTAMPZA ER), 89 (ARYMO ER).
[57] FDA Briefing Information (Addendum), at 3.
[58] Inspirion Briefing Information, at 36.
[59] February 2016 Petition, at 11.
[60] Inspirion Briefing Information, at 11.

a viscous hydrogel, and includes oxycodone at high purity and high label claim.[61] The same can be said of ROXYBOND: [redacted][62] the same extraction techniques—i.e., [redacted]—will also be capable of circumventing the gelling properties of ROXYBOND. Furthermore, the available information suggests that extraction can readily be performed [redacted][63] The pivotal extraction study documented in ARS-122-08 does not address this issue and is therefore incomplete. As such, the study must be considered invalid, and should not have been used as evidence to support approval of the Inspirion NDA.

c. FDA Should Not Rely on HAP ("Liking") Studies Because Such Studies Are Inherently Flawed

In its February 2016 Petition, PMRS requested that FDA "[r]emove Category 3 human abuse-deterrent (liking) studies from the [AD Opioid Evaluation and Labeling] Guidance and as a requirement for approval of drug products with potentially abuse deterrent properties" because liking studies are "inherently flawed, subjective, and highly prone to manipulation."[64] PMRS reiterated this concern in a letter reply to FDA's interim response[65] and during the advisory committee meeting for VANTRELA ER.[66] Notwithstanding the significant concerns raised by PMRS—concerns that are still pending before FDA—the Agency decided to approve the Inspirion NDA, in part, based on the results of a flawed HAP study.

Specifically, the HAP study relied upon by FDA to approve in the Inspirion NDA was inherently flawed because of the substantial difference in the volume of the tablets used in the study. This is because conducting a HAP study with such obvious differences in the drug volume to be insufflated imparts bias into the study by unblinding the subjects. FDA acknowledges as much in its Guidance when it states that "even though subjects might not be able to see the sample, un-blinding may still occur due to the physical properties of samples."[67]

A ROXICODONE 30 mg tablet as used in study O-ARIR-002 has a mass of 100 mg. In comparison, the ROXYBOND 30 mg tablet has a mass of 587 mg, nearly 6 times greater than

[61] February 2016 Petition, at 11.
[62] [redacted]
[63] *Id.*
[64] February 2016 Petition, at 3.
[65] Letter from Edwin R. Thompson, President, Pharmaceutical Manufacturing Research Services, Inc., to Carol J. Bennett, Deputy Director, Office of Regulatory Policy, CDER, Docket No. FDA-2016-P-0645, at 3 (Aug. 25, 2016).
[66] *See, e.g.*, Transcript, Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM), at 135 (Jun. 7, 2016), https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM516486.pdf (last visited May 11, 2017) ("Liking studies are not valid scientific evidence and should not be a requirement for abuse-deterrent labeling, nor should they be used to approve abuse-deterrent labeling.").
[67] AD Opioid Evaluation and Labeling Guidance, at 10.

the ROXICODONE tablet to which it was compared.[68] Conducting a study with such a significant difference in the treatments examined makes it impossible to blind, and is therefore of dubious evidentiary value. This is underscored by FDA's own regulations, which require that "[a]dequate measures are taken to minimize bias on the part of the subjects."[69] Although ROXYBOND's sponsor attempted to eliminate bias by conducting a double-blind, double-dummy, placebo-controlled, single-dose, 4-way crossover study,[70] there is simply no mechanism by which the differences in volume can be completely controlled. Moreover, visual controls—such as the sponsor's use of amber vials and the darkened room lighting—likewise provide no means of controlling the significant differences in tactile perception created by the enormous disparity in volume between treatments.

While the discussion in the Guidance further anticipates that "in some formulations, higher crushed tablet/capsule volume or larger particle size may inhibit complete intranasal administration thereby contributing to the deterrence effects,"[71] if increased volume is, in itself, a significant contributing factor to abuse deterrence, this type of design knowingly introduces bias into the study, violating the key outcomes the study is attempting to measure. It is unreasonable to expect that such a large difference in the volume of insufflated drug will not have an equally large impact on the study results through the bias induced in subjects by unblinding. Therefore, this study does not yield evidence which permits any scientific evaluation, results, or conclusions, and it should not have been a basis for FDA's approval of the Inspirion NDA.

d. FDA Should Require Postmarketing Proof of Abuse-Deterrent Properties Before Approving Abuse-Deterrent Labeling.

In contrast to premarket studies which are designed to *predict* whether a product has abuse-deterrent properties, the goal of postmarket studies is to determine whether the actual marketing of the purportedly abuse-deterrent product did *in fact* result in *meaningful* reductions in abuse.[72] PMRS requested in its February 2016 Petition that FDA "[r]equire 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, 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."[73]

PMRS continues to believe that opioid drug products should not be marketed as abuse-deterrent for a particular route of abuse until there is empirical evidence from postmarketing studies to support such claims. As PMRS noted in its February 2016 Petition, "[n]umerous third party

[68] Inspirion Briefing Information, at 38.
[69] 21 CFR 314.126 (b)(5).
[70] Inspirion Briefing Information, at 12.
[71] AD Opioid Evaluation and Labeling Guidance, at 12.
[72] *Id.* at 17 (emphasis added).
[73] February 2016 Petition, at 3-4 (emphasis added).

reports show [that Reformulated OXYCONTIN] and other similar abuse deterrent formulations have no meaningful abuse deterrence."[74] For example, data from the CDC indicate that the number of overdose deaths due to opioids remains at unacceptably high levels, despite FDA's approval of purportedly abuse-deterrent products (see Figure 6).

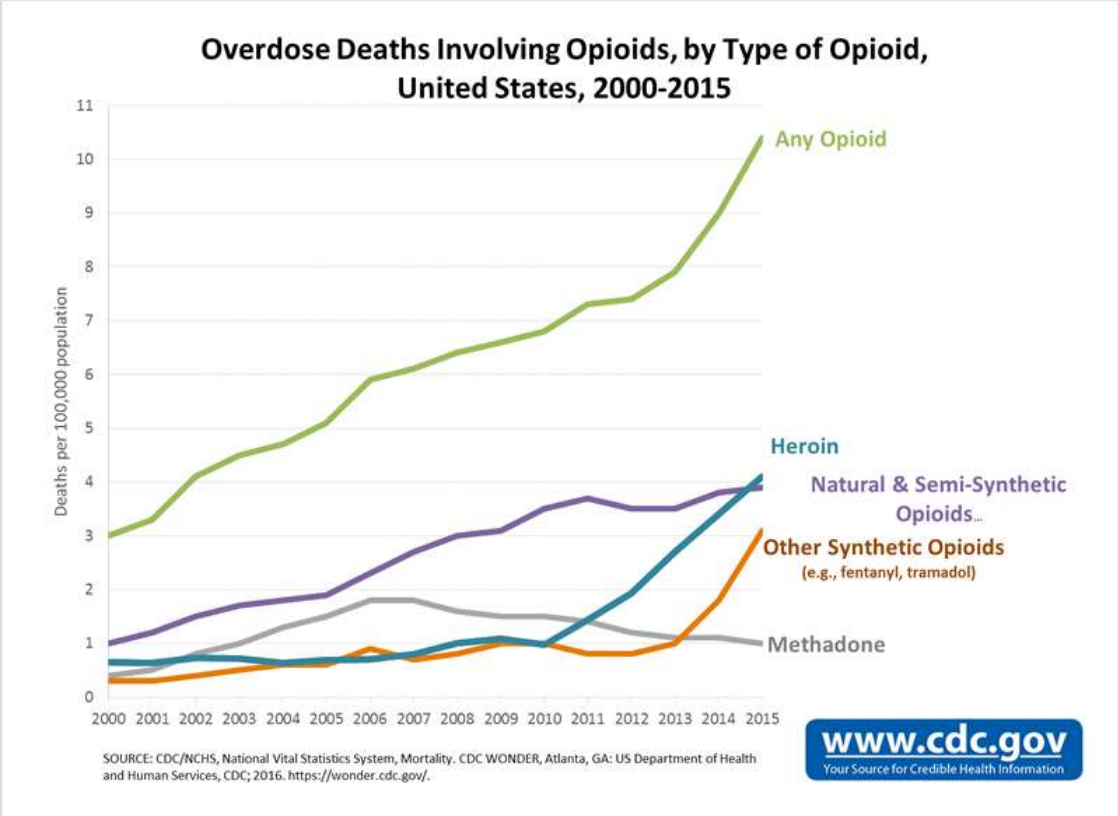

Figure 6 – Overdose Deaths Involving Opioids[75]

To date, FDA has yet to respond substantively to PMRS' request. Notwithstanding this silence, FDA has continued to approve opioid products with abuse-deterrent labeling despite a lack of empirical, real-world evidence to justify the purported safety benefits of allowing these claims. Indeed, as the Director of Epidemiology at CDER opined at the advisory committee meeting for the opioid drug product XTAMPZA ER:

> "[W]e've not seen data that suggests that OxyContin ADF has actually made a meaningful reduction in abuse. . . . So I would just caution that even though what we're looking at here are [premarketing data,] I think the jury is still out as to how well abuse-deterrent formulations have done in the real world, and it's not specific

[74] *Id.* at 19.
[75] March 2017 Petition, at 8 (citing CDC, *Overdose Deaths Involving Opioids*, https://www.cdc.gov/drugoverdose/data/analysis html (last visited May 11, 2017)).

> to OxyContin. It's actually all of them. We just don't have the data we'd like to see yet."[76]

With no response provided in conjunction with the recent approval of the Inspirion NDA, FDA has again declined to provide PMRS with a substantive response on this critical issue.

2. Additional Bases for FDA Stay of Approval of the Inspirion NDA

PMRS requested in its February 2016 Petition that FDA "[r]emove Category 3 human abuse-deterrent (liking) studies from the [Evaluation and Labeling] Guidance and as a requirement for approval of drug products with potentially abuse deterrent properties" because liking studies are "inherently flawed, subjective, and highly prone to manipulation."[77] PMRS continues to strenuously assert that results generated from HAP studies are not valid because these studies are highly subjective and their design is inherently flawed. While FDA should not have relied upon HAP studies to evaluate the purported abuse-deterrent properties of ROXYBOND, PMRS nonetheless believes that there are specific issues with the actual HAP studies that were conducted, which only serve to cast further doubt upon the validity of these results.

a. Inspirion's HAP Study Should Have Used the Manipulation That Causes the Highest Release of the Opioid and the Highest Plasma Levels

A key recommendation in FDA's Guidance is that: "For each relevant route of administration, the potentially abuse-deterrent product and comparator should be manipulated based on the results of Category 1 studies to cause the highest release of the opioid and the highest plasma levels."[78] As PMRS explained in the February 2016 Petition[79] and at the recent advisory committee meeting on Opana ER[80], extraction of opioid from a product, followed by recovery of the opioid in solid form, is the most appropriate method for satisfying this criteria. The feasibility of using this method to extract and then recover solid opioid particles from intact ROXYBOND tablets was previously discussed in section A.1.b(2), *supra*.

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[76] February 2016 Petition, at 18 (quoting Transcript, Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM), at 305-306 (Sep. 11, 2015), https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM478974.pdf (last visited May 11, 2017)).

[77] February 2016 Petition, at 3.

[78] AD Opioid Evaluation and Labeling Guidance, at 12.

[79] February 2016 Petition, at 11.

[80] Transcript, Joint Meeting of the Drug Safety and Risk Management Advisory Committee (DSaRM) and the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC), at 54-58, (Mar. 14, 2017), https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM553191.pdf (last visited May 11, 2017).

Indeed, PMRS recently demonstrated the general applicability of this approach by extracting tablets of another opioid—OPANA ER—and then recovering the opioid in solid form.[81] A key finding of this study was that 97% of the resulting particles were <500 µm—the optimal size and amount of particles expected to increase opioid availability following intranasal administration.[82] By not requiring Inspirion to conduct the HAP study with opioid particles prepared by this known method of extraction, FDA's approval of the Inspirion NDA was contrary to a core principle—i.e., maximization of opioid release and plasma levels—set forth in the Guidance.

The sponsor's intranasal HAP study O-ARIR-002[83] fails to correctly apply the principles established in the FDA Guidance for abuse deterrence evaluation in regards to manipulating the products to cause the highest release of the opioid and the highest plasma levels.[84] This recommendation in the Guidance is eminently reasonable, as a scientific matter, and should be adhered to anytime a HAP study is performed. Abuse deterrence cannot be sufficiently evaluated in Category 2 and Category 3 studies unless the abuse-deterrent formulation has been manipulated to cause the highest release of drug.

As noted above in Section A.1.b(2), the only method to reliably and reproducibly create particles with the highest release and the highest blood levels is by recovering the opioid (API) through extraction.[85] Oxycodone is soluble in common solvents; the extract of a ROXYBOND tablet in solution can potentially be further manipulated to produce solid particles with high label claim and high purity. These particles can then be insufflated or reconstituted for injection in the abusers' preferred media. Using extraction, the drug product is reduced to the smallest particle size which will demonstrate the highest release. This method more robustly challenges and therefore assesses a product's abuse deterrence.

There are three criteria for studying the relevant routes of abuse identified in the Guidance. The study methodology used in support of the Inspirion NDA failed to comply with—or offer a scientifically valid alternative approach for—all three of them:

1. For a product with potential for abuse by the nasal route, the particle size distribution following attempted manipulation by various methods should be established, and the method that provides the smallest particle size should be used in subsequent studies.[86]

[81] PMRS has also demonstrated that this same approach can be used to produce solid opioid particles from Reformulated OXYCONTIN. *See* February 2016 Petition, at 11.
[82] Transcript, Joint Meeting of the Drug Safety and Risk Management Advisory Committee (DSaRM) and the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC), at 56-57, (Mar. 14, 2017), https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM553191.pdf (last visited May 11, 2017).
[83] Inspirion Briefing Information, at 12.
[84] AD Opioid Evaluation and Labeling Guidance, at 12.
[85] February 2016 Petition, at 11.
[86] AD Opioid Evaluation and Labeling Guidance, at 7.

- The sponsor's study did not extract the active pharmaceutical ingredient from the excipients to provide the smallest particle size.

2. For each relevant route of administration, the potentially abuse-deterrent product and comparator should be manipulated based on the results of Category 1 studies to cause the highest release of the opioid and the highest plasma levels.[87]

   - The potentially abuse-deterrent product and comparator were not manipulated to produce an extract which would exhibit the highest release of the opioid and the highest plasma levels.

3. The potentially abuse-deterrent product and comparator study drug should be produced with similar particle size distribution based on a detailed protocol for the preparation of the samples, even if different methods are necessary to do so.[88]

   - The potentially abuse-deterrent product and comparator study drug were not produced with a similar particle size distribution based on a detailed protocol for the preparation of the samples. The sponsor should have extracted both the experimental drug and the comparator to a similar particle size.

Inspirion prematurely stopped the process when determining the product's smallest particle size which would cause the highest release of the opioid. Evaluating the preparation for abuse with the highest release of the drug is the foundation of the Category 2 and Category 3 studies. If the sponsor does not create the smallest particles which will demonstrate the highest release, the studies that rely on this data cannot be deemed to have merit. Solely grinding the product to a particle size distribution composed of 60% by weight, particles greater than 425 microns, is scientifically unreasonable and accordingly misaligned with the Agency's guidance. Inspirion's HAP study O-ARIR-002 failed to manipulate the product to cause the highest release of opioid and is therefore invalid. For this reason, any reliance on the HAP study as support for abuse-deterrent labeling is also invalid and, accordingly, the Inspirion NDA should not have been approved.

b. The Results of Inspirion's HAP Study Indicate Significant Abuse Potential for ROXYBOND

The sponsor of the Inspirion NDA conducted intranasal HAP study O-ARIR-002 to assess the potential deterrence effects of the ROXYBOND tablet. This was a four-way crossover study, evaluating the following treatments: Placebo (microcrystalline cellulose) Intranasal + Oral Placebo, Crushed ROXICODONE 30 mg Intranasal + Oral Placebo, Ground Oxycodone ARIR 30 mg Intranasal + Oral Placebo, and Intact Oxycodone ARIR 30 mg Oral + Intranasal

[87] *Id.* at 12.
[88] *Id.*

Placebo.[89] The primary measure of this study was Drug Liking Visual Analog Scale ("VAS"), with secondary measures of High VAS, Take Drug Again VAS, and Overall Drug Liking VAS.[90] Crushed ROXICODONE 30 mg served as the positive control in this study, which is defined in the Guidance as "an opioid drug product or drug substance expected to result in a predictable opioid drug liking effect and has a known potential for, or history of, abuse."[91]

Contrary to expectations, this study surprisingly demonstrated that un-manipulated ROXYBOND 30 mg administered orally was found to elicit responses almost identical to those of crushed ROXICODONE 30 mg administered intranasally in all measures (see Table 1). The E_{max} means (SD) of Drug Liking for crushed ROXICODONE 30 mg and intact ROXYBOND given orally, were 82.86 (11.55) mm, and 81.48 (11.49) mm, respectively.[92] Furthermore, the E_{max} mean (SD) values for High, Take Drug Again, and Overall Drug Liking for crushed ROXICODONE 30 mg and intact ROXYBOND given orally were likewise almost identical.

	Intact RoxyBond® (Oral)	**Crushed Roxicodone® (Intranasal)**	**Ground RoxyBond® (Intranasal)**
Drug Liking	81.48 (11.49)	82.86 (11.55)	71.14 (12.01)
High	66.66 (25.92)	66.34 (25.67)	39.38 (25.88)
Take Drug Again	77.31 (18.11)	82.14 (16.44)	62.24 (24.51)
Overall Liking	78.55	80.86 (14.60)	64.21 (21.64)

Table 1 – Mean (SD) E_{max} VAS scores for studied drug treatments, reported in mm[93]

As stated by the sponsor, "[s]tatistical analyses of the comparison of intact Oxycodone HCl ARIR 30 mg given orally versus intranasal crushed Roxicodone 30 mg demonstrated no statistically significant differences with respect to Drug Liking (p = 0.53), High (p=0.95), Take Drug Again (p=0.2587), and Overall Drug Liking (p=0.6313)."[94] With crushed ROXICODONE administered intranasally representing a known route of abuse, an equally high Drug Liking VAS for ROXYBOND suggests an equally high potential for abuse. As stated in the Guidance, "[t]he VAS should be the primary measure for drug liking because it appears to correlate most directly with potential for abuse."[95]

[89] FDA Briefing Information, at 106.
[90] *Id*.
[91] AD Opioid Evaluation and Labeling Guidance, at 4 n.6.
[92] FDA Briefing Information, at 107-108.
[93] *Id.*
[94] *Id*. at 108.
[95] AD Opioid Evaluation and Labeling Guidance, at 13.

Furthermore, this study found orally administered ROXYBOND to have a higher C_{max} and earlier T_{max} than crushed ROXICODONE 30 mg given intranasally, which was found to have a C_{max} of 56.5 ng/mL and a median T_{max} of 1.7 hours (see Table 2). In comparison, orally administered ROXYBOND 30 mg was found to have a C_{max} of 58.4 ng/mL and a median T_{max} of 1.3 hours. As stated by the sponsor, "Oral administration of Oxycodone HCl ARIR 30 mg resulted in oxycodone plasma C_{max} of 58.4 ng/mL. This meets the definition of bioequivalence for the C_{max} produced by intranasal ground Roxicodone 30 mg."[96] Much like the Drug Liking VAS, this is startling, as the abuse potential of ROXYBOND administered orally is shown to exceed that of manipulated ROXICODONE. This conclusion can be made directly from the Guidance as "a more rapid onset of action or a shorter time-to-reach peak effect is generally associated with greater abuse potential."[97]

	Intact RoxyBond® (Oral)	**Crushed Roxicodone® (Intranasal)**	**Ground RoxyBond® (Intranasal)**
C_{max} (ng/mL)	58.4	56.5	42.7
T_{max} (hours)	1.3	1.7	2.3

Table 2 – Plasma C_{max} and T_{max} for the studied drug treatments[98]

The results of this study provide evidence that intact ROXYBOND administered orally is of equal or greater abuse potential when compared to crushed ROXICODONE taken intranasally. Although ground ROXYBOND was found to be statistically different from crushed ROXICODONE, it is necessary to evaluate the results of oral ROXYBOND in this same context to understand the differences in liking and abuse potential between all forms of the studied drug. Despite oral ROXYBOND being intact and unmanipulated, it is statistically similar to the ROXICODONE prepared for abuse and misuse in all studied measures of liking.[99] Unmanipulated ROXYBOND was likewise found to be similar to manipulated, crushed ROXICODONE in the measured plasma C_{max}, to the point of establishing bioequivalence between these two treatments.[100] Therefore, it must be concluded that ROXYBOND in its intact, oral form, and manipulated ROXICODONE abused intranasally are equivalent treatments. It is undeniable that this represents a significant risk to public health, especially because ROXYBOND displays a lack of *meaningful* abuse deterrence.

B. ACTION REQUESTED

[96] FDA Briefing Information, at 108.
[97] AD Opioid Evaluation and Labeling Guidance, at 14.
[98] FDA Briefing Information, at 108.
[99] *Id.* at 107-108.
[100] *Id.* at 108.

PMRS requests that the Commissioner stay the effective date of the approval of NDA 209777 with labeling claims pertaining to (1) chronic use; and (2) abuse deterrence until FDA issues a substantive written response to the citizen petitions submitted by PMRS on February 19, 2016 and March 6, 2017 and to the issues raised in this petition.

C. STATEMENT OF GROUNDS

FDA's regulation at 21 CFR § 10.35(e) sets out the standard for review of a petition for stay of action. Pursuant to Section 10.35(e), FDA is required to grant a petition for stay when, as here, the petitioner satisfies the following four elements:

(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 the stay;

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

For the reasons discussed below, PMRS's petition for stay satisfies each of the four required elements. Therefore, PMRS respectfully submits that its petition for a stay must be granted in accordance with Section 10.35(e).[101]

1. PMRS Will Suffer Irreparable Injury in the Absence of a Stay

The launch of ROXYBOND prior to FDA's consideration of the PMRS Petitions will cause irreparable injury to PMRS on two grounds. First, 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. As a result, PMRS, which has developed an immediate-release 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

[101] Pursuant to 21 C.F.R. § 10.35(e), FDA also has the discretionary authority to grant a petition for a stay if it is "in the public interest and in the interest of justice." Having established each of the elements necessary to trigger a mandatory stay under 21 C.F.R. § 10.35(e), PMRS respectfully submits that it also has met -- and exceeded -- the threshold needed to permit FDA to utilize its discretionary authority to grant a stay. As discussed in Section C.3 and C.4, *infra*, a stay is needed to protect the public health. Moreover, it is in the interest of justice to allow the information contained in PMRS's pending Petitions to be reviewed before any additional opioid products labeled with claims of abuse deterrence or chronic use are approved by FDA. Thus, PMRS respectfully submits that even if FDA ultimately determines that a mandatory stay is not required, FDA nevertheless should use the discretion afforded to it under 21 C.F.R. § 10.35(e) to grant PMRS's petition for a stay.

on the marketplace in relation to other appropriately studied and labeled IR products formulated with "abuse-deterrent" properties.[102]

Second, the launch of ROXYBOND will have an immediate and significant impact upon the market and on PMRS's investment in research and development, particularly in light of the current public discourse about the dangers of opioid abuse. In turn, PMRS will be forced to compete for market opportunities with a manufacturer whose product labeling includes unsupported claims that risk creating confusion with adverse consequences to the public health. PMRS will not be able to recoup its losses from FDA or any other individual or entity. Accordingly, PMRS will suffer irreparable injury absent a temporary stay to allow FDA to fully consider and respond to the issues raised in PMRS's pending Petitions and to the issues raised herein.

It is axiomatic that the wrongful launch of a drug significantly erodes market share, market opportunities, potential client base, and revenue. "Courts have recognized that … diminished market share can constitute irreparable harm."[103] Indeed, the loss of market opportunities constitutes evidence of irreparable harm.[104]

In *Bayer*, for example, the Court explained the critical interplay between the market and the petitioner. Bayer argued that the approval of Enroflox would have a negative effect on its market share.[105] Bayer argued that without a temporary restraining order, it would be irreparably harmed by "deep drops in revenues, loss of valuable customer relationships, loss of research and development funds, and fewer revenue-generating future products in the pipeline."[106] Thus, in *Bayer*, the Court confirmed that Bayer had demonstrated the risk of irreparable harm by alleging that a competitor's entry into the marketplace would dilute market share and cause loss of customer good will, and cause loss of research and development funding.

Courts have explained that the irreparable harm caused by such market dilution exists even when other similarly situated products already are in the marketplace.[107] For example, in *Abbott Labs*, Sandoz argued that the harm to Abbott Labs was not, as a matter of law, irreparable because

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[102] *See, e.g., Hill Dermaceuticals, Inc., v. FDA*, 524 F. Supp. 2d 5, 12 (D.C. 2007).

[103] *Bayer HealthCare, LLC v. U.S. Food & Drug Admin.*, 942 F. Supp. 2d 17, 26 (D.D.C. 2013) (citing *Purdue Pharma L.P. v. Boehringer Ingelheim GmbH*, 237 F.3d 1359, 1368 (Fed. Cir. 2001) (likelihood of price erosion and loss of market position are evidence of irreparable harm); *Polymer Technologies, Inc. v. Bridwell*, 103 F.3d 970, 975–76 (Fed. Cir. 1996) (explaining how loss of market opportunities constitutes evidence of irreparable harm); *Bio–Technology Gen. Corp. v. Genentech, Inc.*, 80 F.3d 1553, 1566(Fed. Cir. 1996) (loss of revenue, goodwill, and research and development constitutes irreparable harm); *Collagenex Pharmaceuticals, Inc. v. Thompson*, No. CIV.A. 03-1405(RMC), 2003 WL 21697344, at *10 (D.D.C. July 22, 2003), *as amended* (Aug. 26, 2003), *order dissolved sub nom. Collagenex Pharm., Inc. v. Thompson*, No. CIV.A.03-14-5(RMC), 2005 WL 256561 (D.D.C. Jan. 19, 2005)); *but see Biovail Corp. v. U.S. FDA*, 519 F. Supp. 2d 39, 49 (D.D.C. 2007); *Mylan Pharm., Inc. v. Shalala*, 81 F.Supp.2d 30, 42–43 (D.D.C.2000); *Bristol-Myers Squibb Co. v. Shalala*, 923 F. Supp. 212, 221 (D.D.C. 1996).

[104] *Polymer Technologies, Inc.*, 103 F.3d at 975–76 (Fed. Cir. 1996).

[105] *Id.* at 25.

[106] *Id.*

[107] *Abbott Labs. v. Sandoz, Inc.*, 544 F.3d 1341, 1361–62 (Fed. Cir. 2008).

there were damages available for infringement and because other generic companies already had launched their versions of the reference listed drug at issue.[108] The Court flatly rejected Sandoz's argument, concluding that the presence of other companies diluting market share and triggering revenue loss did not negate the market share and revenue loss claims that Abbott Labs had asserted against Sandoz.[109] Accordingly, the *Abbott Labs* Court granted the motion to stay.

In our case, the alleged harm is even more pronounced than the harm in *Bayer* and *Abbott* because, unlike in those cases, Inspirion's opioid product has not yet been demonstrated to have efficacy as a treatment for chronic pain or to possess meaningful abuse-deterrent properties. As discussed at length in section A., *supra*, the methodology, data and information relied upon for approval of the Inspirion NDA is fatally flawed. In turn, its labeling contains information that risks misleading the public into believing that the science behind ROXYBOND shows that ROXYBOND has been proved to be an abuse-deterrent opioid and that use for chronic pain is appropriate (see, *infra*, Section C.3).

Moreover, it is a matter of public record that ROXYBOND will not be required to incorporate a Risk Evaluation and Mitigation Strategy ("REMS") into its labeling for some months after its launch because immediate release opioids have not yet been, but are soon expected to be, incorporated into FDA's opioid's program.[110] Because companies like PMRS ostensibly will be required to include a REMS at launch, the public will be led to believe that ROXYBOND is somehow superior to those IR abuse-deterrent opioids that are approved in the next few months, after the REMS program for such products has been adopted.[111]

Additionally, FDA's refusal to stay the approval of the Inspirion NDA until a scientifically rigorous evaluation of the product's efficacy and safety has been completed will further injure PMRS because of the distinct disadvantages associated with not being the first market entrant.[112] First, PMRS will face an increased risk that its proposed product will be held to an inappropriate approval standard based on the precedent set by the approval of the Inspirion NDA. As FDA unequivocally states in its guidance on evaluating abuse-deterrent opioid products, "[t]he standard against which each product's abuse-deterrent properties are evaluated *will* depend on

[108] *Id.*
[109] *Id.*
[110] FDA, Sharon Hertz, M.D., *FDA Plan: Opioid Analgesic Education*, slide 2, 15 (Jan. 25, 2017), https://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm536125.htm (last visited May 11, 2017). The presentation noted that the Advisory Committee convened to consider this issue advised adding the "immediate-release (IR) opioid analgesic products to the ER/LA Opioid Analgesics REMS." Regarding the timeline, the presentation suggested the "[p]otential addition of IR sponsors in the RPC by fourth quarter 2017" and that FDA would "notif[y] all sponsors in first quarter 2018 of modified REMS."
[111] Although once REMS has been adopted, all IRs would be subject, the launch of one without and those subsequently approved with (due to timing) risks a prejudicial effect.
[112] *See Mova Pharm Corp. v. Shalala*, 140 F.3d 1060, 1066 n.6 (D.C. Cir. 1998) ("[T]he district court found that Mova would be harmed by the loss of its 'officially sanctioned head start' and that Mova's small size put it at a particular disadvantage. This suffices to show a severe economic impact to Mova.").

the range of abuse-deterrent and non-abuse-deterrent products on the market at the time of that application."[113]

Second, PMRS faces a real risk that its product will be inappropriately compared to other abuse-deterrent products—such as the Inspirion NDA—whose approvals were based on limited evidence of efficacy or meaningful abuse-deterrent properties. Indeed, FDA states in the guidance that it "expects sponsors to compare their formulations against approved abuse-deterrent versions of the same opioid" and that these "comparisons should be based on the *relevant* categories of testing."[114] Since FDA has so far declined to substantively respond to the PMRS Petitions seeking clarification on the Agency's testing recommendations, PMRS has been deprived of the necessary information it needs to properly mitigate, or respond to, these foreseeable harms.

Last, PMRS will also face an increased risk of being subject to procedural disadvantages associated with the approval process for its own proposed product. For example, the Inspirion NDA was able to avail itself of priority review status, presumably due to it being the first to seek approval as an abuse-deterrent IR opioid. Thus, it is reasonable to expect that FDA might decline to grant priority review status to subsequent market entrants.

In sum, FDA's approval of the Inspirion NDA while failing to provide PMRS with a substantive response to its pending Petitions and the issues raised herein would result in ROXYBOND holding a privileged position in the marketplace, effectively tainting the market for researchers and developers such as PMRS.[115] That outcome would be fundamentally unfair and, as the operative case law has confirmed, would result in irreparable harm to PMRS. Therefore, PMRS has established that it will suffer irreparable harm if its petition for a stay is not granted, satisfying the first required element for a stay set forth in 21 CFR § 10.35(e)(1).

2. PMRS's Case Is Not Frivolous and Is Being Pursued in Good Faith

PMRS's Petition for Stay is not frivolous and is being pursued in good faith. Its Petition is predicated, in part, upon PMRS's two pending petitions, both of which also are not frivolous and are being pursued in good faith, having been grounded in substantive scientific and legal arguments. Indeed, FDA has acknowledged, in its interim response to PMRS's February 2016 Petition, that the Agency "has been unable to reach a decision on [PMRS's] petition because it

[113] AD Opioid Evaluation and Labeling Guidance, at 3 (emphasis added).
[114] *Id.* at 23 (emphasis added); *see also* Robert M. Califf et al., *A Proactive Response to Prescription Opioid Abuse*, 374 New Eng. J. Med. 1480, 1483 (2016) ("The availability of abuse-deterrent formulations raises questions, including … whether to modify criteria for the review and approval of oral opioid formulations that … do not offer advantages in abuse deterrence *relative to currently marketed products*." (emphasis added)).
[115] We note that PMRS has a New Drug Application pending for an immediate release abuse-deterrent drug. Though PMRS is not yet in the market, the irreparable harm to market share and to revenue greatly impacts PMRS's calculus attendant to bringing a product to market. Thus, to be clear, PMRS will suffer irreparable harm, even while its NDA is pending before FDA.

raises complex issues requiring extensive review and analysis by Agency officials." [116] Concurrent with the filing of these petitions, PMRS has also consistently raised these issues in good faith at numerous public meetings pertaining to opioid drug products.[117]

Despite PMRS's good faith attempts to obtain clarification on these issues, FDA has declined to issue a substantive response on the PMRS Petitions while at the same time continuing to approve opioid drug products with abuse-deterrent labeling.[118] As discussed in detail in Section A., *supra*, FDA's recent approval of the Inspirion NDA conflicts with the issues raised in the PMRS Petitions. Thus, the Agency should have provided PMRS with a substantive response to those petitions on, or before, the date on which it approved the Inspirion NDA. For these reasons, PMRS's case is not frivolous and is being pursued in good faith.

3. PMRS Has Demonstrated Sound Public Policy Grounds Supporting the Stay

Sound public policy requires that the requested stay be granted because it is FDA's charge to ensure that the drugs used by the U.S. public are both effective and safe for their labeled uses. The overarching purpose of FDA's new drug approval provisions is "to establish an efficient and thorough drug review process in order to … [f]acilitate the approval of drugs shown to be safe and effective[and] *ensure the disapproval of drugs not shown to be safe and effective*."[119] At their core, the PMRS Petitions raise fundamental questions about both the efficacy and safety of opioid drug products, especially those products with purportedly abuse-deterrent claims. For this reason, 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.

In its March 2017 Petition, PMRS requested that FDA revoke approval of all labeling that supports the use of opioids in the treatment of chronic pain. As summarized in Section A.1.a, *supra*, PMRS has consistently questioned the efficacy of opioid drug products for the treatment of chronic pain because this use has not been established by substantial evidence. For example, PMRS has observed that "in violation of the Federal Food, Drug, and Cosmetic Act, the FDA has added supporting labeling for chronic treatment for immediate-release opioids despite the lack of substantial evidence of efficacy and safety."[120] Accordingly, it is contrary to FDA's stated public policy mission to approve the Inspirion NDA with labeling that supports the

[116] Letter from Carol J. Bennett, Deputy Director, Office of Regulatory Policy, CDER, to Edwin R. Thompson, President, Pharmaceutical Manufacturing Research Services, Inc., Docket No. FDA-2016-P-0645, (Aug. 16, 2016).
[117] *See generally* PMRS's comments at the advisory committee meetings pertaining to VANTRELA ER (Jun. 7, 2016), TROXYCA ER (Jun. 8, 2016), ARYMO ER (Aug. 4, 2016), the use of opioids in pediatric patients (Sep. 16, 2016), OPANA ER (Mar. 14, 2017), and ROXYBOND (Apr. 5, 2017) as well as the public meeting on premarket evaluation of abuse-deterrent properties (Nov. 1, 2016).
[118] Since PMRS filed its February 2016 Petition, FDA has approved the following opioid drug products with abuse-deterrent labeling: XTAMPZA ER, VANTRELA ER, TROXYCA ER, ARYMO ER, and ROXYBOND.
[119] 21 C.F.R. § 314.2 (emphasis added).
[120] March 2017 Petition, at 4 (citing ROXICODONE Highlights of Prescribing Information (Rev.: 12/16/2016) , Dosage and Administration, https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021011s006lbl.pdf (last visited May 11, 2017)).

efficacy of this product for the treatment of chronic pain because this use has never been adequately investigated.[121]

In addition, the effectiveness of an opioid product's abuse-deterrent properties necessarily affects the product's overall abuse potential and is, thus, a key aspect that FDA should consider when determining whether a proposed product is safe for approval. In its February 2016 Petition, PMRS requested that FDA adhere to its own recommendations for evaluating Category 1 premarket studies to ensure that the abuse potential of opioid products with abuse-deterrent labeling—and, by extension, their safety profile—was established in a scientifically rigorous manner before such products were approved. PMRS also requested that FDA remove HAP studies as a premarket requirement for abuse-deterrent labeling because the design of these studies is inherently flawed and, thus, provides unreliable evidence regarding the actual abuse potential of these products. Given that a proposed product's abuse potential is a function of its actual abuse-deterrent properties, PMRS submits that it is not sound public policy to approve the Inspirion NDA with abuse-deterrent labeling until the abuse-deterrent properties of the product are assessed in a scientifically rigorous manner, based on the principles set forth in the Guidance as well as real-world data collected from postmarketing studies.

Moreover, FDA's approval of the Inspirion NDA without responding to the PMRS Petitions violates fundamental principles of the Administrative Procedure Act (APA). Under the APA, an agency is required to "have considered relevant data and articulated an explanation establishing a 'rational connection between the facts found and the choice made.'"[122] FDA's approval of another opioid product with the same underlying significant substantive issues raised in heretofore unanswered PMRS petitions is arbitrary, capricious and otherwise not in accordance with the law.[123] Finally, the Agency's approval of the Inspirion NDA prior to responding to the PMRS Petitions also runs afoul of FDA's own well-established practices. Indeed, it is FDA's regular practice to respond to pending petitions prior to, or simultaneous with, taking related action.[124]

In sum, the public policy grounds supporting the stay are overwhelming.

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[121] *See* FDA, What We Do: FDA Mission, https://www fda.gov/aboutfda/whatwedo/ ("The Food and Drug Administration is responsible for protecting the public health by ensuring the safety, efficacy, and security of human and veterinary drugs, biological products, and medical devices …") (last visited May 11, 2017).
[122] Bayer Healthcare at *9 (citing *Bower v. Am. Hosp. Ass'n*, 476 U.S. 610, 626 (1986)).
[123] *See* 5 USC 706(2)(a); see also *Public Citizen v FAA*, 88 F.2d 186, 197 (D.C. Cir. 1993) (describing the legal requirement that "agency action not be arbitrary or capricious include a requirement that the agency adequately explain its result.")
[124] *See, e.g.*, Letter from Janet Woodcock, M.D., Director, CDER, to Betty Mekdeci, Birth Defect Research for Children, Inc., Docket No. 1992-P-0494, at 4 (Aug. 15, 2013), https://www regulations.gov/document?D=FDA-1992-P-0494-0001 (last visited May 11, 2017) (describing agency delay in issuing a formal response as largely as oversight).

4. Any Delay Resulting from the Stay is Not Outweighed by Public Health or Other Public Interests

Any delay that results from a stay of the effective date of the Inspirion NDA is, on balance, not outweighed by public health or other public interests. In fact, a stay of the effective date of the Inspirion NDA would serve to further protect the public health interest by ensuring that additional opioid drug products are not prematurely added to the market before their efficacy safety is adequately established in a scientifically rigorous manner. Several considerations favor this conclusion.

First, there is strong public interest in assuring that FDA's approval of opioid drug products with abuse-deterrent labeling does not provide prescribers and patients with a false sense of security about the actual abuse potential of these products. Paradoxically, the ability to market purportedly abuse-deterrent opioid products before their actual effectiveness—including, a *meaningful* reduction in abuse potential—is established by postmarketing studies has the potential to *increase*—not reduce—the rate at which these products are prescribed.

Statements from medical professionals at advisory committee meetings held to discuss the approval of opioid drug products with abuse-deterrent labeling suggest that these concerns are not merely theoretical. As one member noted at the OPANA ER meeting, "while well intentioned, having drug-deterrent indications in the label actually led to unintended consequences. I think it gave physicians a sense of false security that the drug that they were prescribing had less abuse potential when in fact we saw what the outcome of this was."[125] This sentiment was echoed by another medical professional who spoke at the hearing:

> The other problem is the unintended consequence that the term abuse deterrent will give prescribers a false sense of security so that they won't worry so much about causing abuse or addiction. Abuse deterrent will more than anything be a marketing term that will lower the threshold for prescribing. It will clearly lead to more prescriptions. And it's likely that that is an intended consequence by the manufacturer. But more prescriptions will predictably lead to more abuse and addiction and more deaths.[126]

In a similar vein, at the VANTRELA ER advisory committee meeting, one member commented that:

> We should think about the potential downside of [granting abuse-deterrent labeling to opiates] and whether we are giving or lowering the bar of prescribing

[125] Transcript, Joint Meeting of the Drug Safety and Risk Management Advisory Committee (DSaRM) and the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC), at 259 (Mar. 14, 2017), https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM553191.pdf (last visited May 11, 2017).
[126] *Id.* at 103-104.

> long-acting opiates in general by providing this, in a sense, marketing tool of abuse deterrence and giving the impression that these drugs might be safer generally beyond that.[127]

Similar opinions have been expressed in discussions surrounding the approval of other opioid drug products.[128]

Second, as detailed in the PMRS Petitions, there is a raging opioid epidemic currently plaguing the United States. Indeed, FDA recently acknowledged that the Agency continues "to be deeply concerned about the growing epidemic of opioid abuse, addiction, and overdose — an epidemic directly related to the increasingly widespread misuse of powerful opioid pain medications."[129] The types of concerns raised by PMRS have also been raised by a diverse group of stakeholders including federal and state officials.[130] And the daily news is replete with articles about the abuse of opioids and the skyrocketing toll it is taking on public health. While PMRS certainly appreciates FDA's intent to do something to help curb abuse, we respectfully suggest that FDA's actions, to date, have been misdirected and risk causing significant unintended consequences to the public health.

Last, it should be noted that not only did FDA approve the Inspirion NDA without responding to the PMRS Petitions, it did so in breathtaking time: a mere 10 business days after the Advisory Committee meeting.

While PMRS recognizes the general benefit of increased choice in the marketplace, such benefit is contingent upon the particular product approved. In this case, the standards used to approve abuse-deterrent labeling for the Inspirion NDA, and the underlying data and information submitted to support such labeling, in addition to labeling that supports use for chronic pain, do not confer benefit to the public interest. In fact, the approval has the opposite effect: it risks harm to the public interest, including first and foremost the patients who are prescribed that drug.

FDA provides a false sense of security to prescribers and patients by approving products with abuse-deterrent labeling under the FDA's current regulatory framework, and facilitates the inclination of many physicians to prescribe opioid products for any chronic pain, rather than

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[127] Transcript, Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM), at 174 (Jun. 7, 2016), https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM516486.pdf (last visited May 11, 2017).

[128] *See, e.g.*, FDA, Anjelina Pokrovnichka, *History of OxyContin: Labeling and Risk Management Program*, slide 12 (Nov. 13, 2008), https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndLifeSupportDrugsAdvisoryCommittee/UCM248776.pdf (last visited May 11, 2017) (noting that "[l]abel language suggesting that OxyContin had lower abuse potential may have impacted product use or prescribing").

[129] Robert M. Califf et al., *A Proactive Response to Prescription Opioid Abuse*, 374 New Eng. J. Med. 1480, 1480 (2016).

[130] *See, e.g., supra* note 8 (remarks of recently confirmed FDA Commissioner Scott Gottlieb, M.D.).

appropriately limiting such prescribing to certain patients.[131] The broad use of opioid products for chronic pain lacks substantive clinical merit and is a well-established springboard to addiction.

Put simply, whatever delay is created by FDA issuing a written response to the PMRS Petitions is not outweighed by any public health or other public interest.

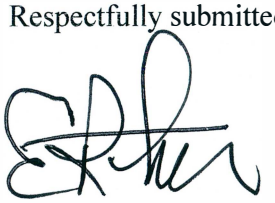
D. CERTIFICATION

After carefully considering the issue, the undersigned has concluded that 21 USC § 355(q) is not applicable to this petition. This conclusion is based on the fact that, to the best of PMRS's knowledge and belief, this petition does not specifically reference a "pending" ANDA or 505(b)(2) nor does a "pending" ANDA or 505(b)(2) relate to the subject matter of this petition.

E. CONCLUSION

For the foregoing reasons, PMRS requests that the Commissioner stay the effective date of the approval of NDA 209777 with labeling claims pertaining to (1) chronic use; and (2) abuse deterrence until the FDA issues a substantive written response to the citizen petitions submitted by PMRS on February 19, 2016 and March 6, 2017 and to the issues raised in this petition.

Respectfully submitted,



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[131] *See supra* note 10.