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Daiichi-Sankyo

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Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: Docket No: FDA-2017-P-3064: Comments of Daiichi Sankyo on PMRS Citizen Petition to Stay the Effective Date of Approval of the NDA (209777) for RoxyBond™ (oxycodone hydrochloride) Tablets

Daiichi Sankyo, Inc. ("Daiichi Sankyo") respectfully submits these comments in response to the above-referenced Pharmaceutical Manufacturing Research Services, Inc. ("PMRS") Petition for Stay of Action ("the Petition"), which requests that the Food and Drug Administration (FDA) stay the effective date of approval for RoxyBond™ (oxycodone hydrochloride) tablets, New Drug Application (NDA) 209777, submitted by Inspirion Delivery Sciences, LLC ("Inspirion") and approved by FDA on April 20, 2017. Daiichi Sankyo is dedicated to the responsible development and marketing of innovative pharmaceutical products to address diversified, unmet medical needs of patients, including the millions of Americans who need pain management treatment. As detailed below, the PMRS Petition lacks scientific merit or a legitimate legal or policy basis, and should be denied by the Agency without delay.

As FDA is well aware, the ongoing opioid abuse epidemic has claimed the lives of tens of thousands of Americans and has adversely affected hundreds of thousands of families. Despite significant efforts to create awareness and reduce opportunities for abuse of opioids through risk mitigation measures, in 2015 alone, 22,000 deaths involved prescription opioids, equivalent to about 62 deaths per day. Abuse-deterrent formulations of opioids are a critical part of the overall solution to this problem. The deployment of such technologies aligns both with FDA guidance and with the Administration's focus on combating opioid addiction and abuse, including but not limited to the White House's Commission on Combating Drug Addiction and the Opioid Crisis;[1] FDA's Opioids Action Plan;[2] FDA's April 2015 Guidance for Industry entitled, "Abuse-Deterrent Opioids — Evaluation and Labeling" (hereafter "AD Guidance"); and FDA's Safe Use Initiative, including the Opioid Patient-prescriber Agreement Working Group.[3]

On April 20, 2017, FDA approved RoxyBond for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate. Section 9.2 of

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[1] *See* https://www.whitehouse.gov/the-press-office/2017/03/30/presidential-executive-order-establishing-presidents-commission (Mar. 29, 2017).

[2] *See* https://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm484714.htm.

[3] Other government-led initiatives to combat opioid abuse include, but are not limited to: the National Academies of Sciences, Engineering, and Medicine (NASEM) comprehensive report and recommendations on the opioid epidemic; the Centers for Disease Control and Prevention (CDC) Prescription Drug Overdose: Prevention for States program; the Substance Abuse and Mental Health Services Administration's (SAMHSA) Opioid Overdose Prevention Toolkit; and various state led initiatives such as prescription drug monitoring programs

RoxyBond's prescribing information provides that RoxyBond has increased resistance to cutting, crushing, grinding, or breaking using selected tools. In addition, the intact and manipulated tablets resisted extraction in selected household and laboratory solvents under various conditions, including selected pre-treatments. Relative to oxycodone immediate-release (IR) tablets, the RoxyBond formulation forms a viscous material that resists passage through a needle, and it was also more difficult to prepare solutions suitable for intravenous injection. 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. Compared to crushed intranasal oxycodone IR tablets, intranasal administration of crushed RoxyBond was associated with statistically significant lower drug liking and take drug again scores.

Following the FDA's approval, Daiichi Sankyo decided to commercialize RoxyBond as part of a license and co-marketing agreement with Inspirion. Daiichi Sankyo recognizes the important role that pharmaceutical manufacturers must play in combating the opioid abuse epidemic. It is for this very reason that Daiichi Sankyo has collaborated with Inspirion to bring to market the first abuse deterrent IR opioid approved by FDA under the agency's abuse deterrent framework. This collaboration demonstrates not only Daiichi Sankyo's commitment to addressing the opioid epidemic, but also to filling the specific unmet medical need for abuse-deterrent IR products, which are prescribed at a much higher rate to patients in the U.S. than extended-release (ER) products.

As explained below, FDA's approval of RoxyBond was sound and fully supported by the underlying medical and scientific data. Those data demonstrated that RoxyBond tablets are resistant to common forms of manipulation and abuse, and the PMRS Petition essentially repackages information that FDA fully considered during the RoxyBond approval process. Indeed, PMRS representatives testified about their concerns to the Anesthetic and Analgesic Drug Products ("AADPAC") and Drug Safety and Risk Management ("DSaRM") Advisory Committees considering RoxyBond, and those committees considered and addressed the issues PMRS raised. We do not intend to respond to every aspect of the PMRS Petition. Moreover, it would not be appropriate for Daiichi Sankyo to address certain of the PMRS claims in a public forum because they involve disclosure of proprietary information regarding abuse-deterrent technologies and study methodologies, which must be kept confidential to prevent potential abusers from obtaining confidential knowledge about RoxyBond's abuse-deterrent properties.

We respond below to the key points raised in the Petition, and we appreciate the FDA's consideration of these comments.

I. FDA's Approval of RoxyBond -- the First Abuse-Deterrent IR Opioid -- Represents a Significant Advance in FDA's Abuse-Deterrent Framework and Helps Address a Critical Unmet Need for Patients and Prescribers

RoxyBond is the first IR opioid approved under FDA's comprehensive abuse deterrent framework and represents a significant advance in fighting opioid abuse and offering prescribers and patients alike a strong tool to combat this tragic epidemic. FDA's approval correctly validated that the abuse-deterrent science and technology underlying RoxyBond comports with the methodologies outlined in FDA's AD Guidance. At the same time, FDA's approval helped

to fill a critical unmet need given how many prescriptions U.S. healthcare professionals write each year for IR products.

In fact, in his brief time as FDA Commissioner, Dr. Scott Gottlieb has repeatedly emphasized the crucial role played by abuse-deterrent IR opioids. For example, Dr. Gottlieb emphasized in July 2017 that:

> Reducing the scope of the epidemic of opioid addiction is my highest immediate priority as Commissioner … The FDA strongly supports a transition from the current market dominated by conventional opioids to one in which the majority of opioids have meaningful abuse-deterrent properties.[4]

In addition, Dr. Gottlieb has announced several new initiatives that FDA plans to undertake to stem the opioid abuse epidemic, including updating the existing Risk Evaluation and Mitigation Strategies (REMS) on ER opioids and extending these same regulatory requirements to IR opioid products.

The April 2017 Advisory Committee meeting for RoxyBond focused on the widespread use of IR products for pain management, and thus the critical need for abuse-deterrent IR opioids. For example, Dr. Richard Dart, Director of the Rocky Mountain Poison & Drug Center and Executive Director of the Researched Abuse, Diversion and Addiction Related Surveillance ("RADARS®") System, discussed the significant number of patients prescribed IR opioids. Dr. Dart noted that, in 2016 alone, there were 151 million prescriptions for IR opioids, "none of which are abuse-deterrent," when compared to just 12 million prescriptions for ER opioids.[5] Dr. Dart testified that data from RADARS showed that "immediate-release opioids are involved in abuse cases more than 4 times as often as extended-release products;" and that "the rate of diversion is six times greater with" IR than ER opioids.[6] Dr. Dart emphasized that abusers "report actually preferring immediate-release over" ER products. He cited to several studies that "have found that most individuals who abuse prescription opioids initiated their abuse with an immediate-release product."[7] Based on the evidence presented, Dr. Dart concluded:

> In summary, I really think it is time to address the need for immediate-release opioids. We need abuse-deterrent properties. Immediate-release opioids are much more commonly prescribed, more commonly abused, and more commonly diverted than

[4] FDA, *Statement from FDA Commissioner Scott Gottlieb, M.D., on National Academies of Sciences, Engineering, and Medicine report on pain management and prescription opioid abuse* (Jul. 13, 2017), *available at* https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm566958.htm.

[5] FDA, Transcript of the Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM)(hereafter "AdComm Transcript")(Apr. 5, 2017) at 39. Dr. Dart also noted that there were "17.9 million immediate-release prescriptions just for single entity oxycodone products, about 50 percent more than all extended-release prescriptions combined." *Id*.

[6] AdComm Transcript at 39-40.

[7] *Id*. at 40 (also citing a study of 300 opioid abusers, which showed that 66% reported a preference to IR opioids versus only 4% who preferred ER).

> extended-release opioids. Immediate-release single entity oxycodone in particular is commonly abused by high-risk intranasal and intravenous routes, which are associated with greater risk of death and other serious health consequences.[8]

The recently published peer-reviewed research in *PLOS ONE* further confirmed the critical need for an abuse deterrent IR product. Using data from RADARS, the study found that, between 2009 and 2015, IR products "account[ed] for 90% of the opioid analgesic prescriptions dispensed," and that IR opioids were prescribed at a 12 to 16 times greater frequency than ER opioids, and that 3 to 7 times more grams were dispensed for IR opioids as compared to ER opioids.[9]

Not surprisingly given these statistics, the study concluded that "rates of prescription opioid abuse were markedly higher for IR than ER medications." For example, the research found that the population-adjusted rate of intentional abuse for IR products in the fourth quarter of 2015 was 4.6 times greater ($p<0.001$) than ER products (0.160 per 100,000 population (95% CI 0.145-0.176) for IR vs. 0.035 (95% CI 0.029-0.042)). The authors further concluded that "high rates of IR abuse have significant public health implications in addressing the opioid epidemic" and reaffirmed the direct relation between "increased drug availability and increased abuse."[10] This conclusion is critically important to FDA's abuse-deterrent framework, as well as related opioid-abuse efforts, because "[i]mpeding IR abuse has the potential to halt the natural progression of medication abuse and addiction at a much earlier stage."[11]

Treatment protocols for acute pain often initially include an IR opioid. If chronic treatment becomes necessary, physicians may prescribe an ER product. Because a "significant portion of the population of patients with pain ha[ve] predisposing factors for addiction," the absence of abuse-deterrent formulations of IR products has unfortunately led some patients to abuse and/or addiction, which in turn, is a gateway to more harmful addiction and abuse of ER or other opioid products. As Dr. Gottlieb himself recognized, "[m]ost exposure to opioid drugs comes from the immediate release formulations," which "serve as the gateway for patients and non-patients who may continue to use or misuse these products" and can "lead to a lot of new addiction." While federal and state policy makers have made important advances regarding abuse-deterrent ER products, up until RoxyBond's approval, they had not previously approved an IR pain management product with an abuse deterrent technology. RoxyBond's approval thus marks an important step to advance abuse-deterrent IR formulations under FDA's framework.

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[8] *Id*. at 42.

[9] J. Iwanicki et al., *Abuse and Diversion of Immediate Release Opioid Analgesics as Compared to Extended Release Formulations in the United States*, PLOS One 11 (12) (Dec. 9, 2016), *available at* http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0167499.

[10] *Id*. (citing Dasgupta N, Kramer ED, Zalman MA, Carino S Jr, Smith MY, Haddox JD, et al. Association between non-medical and prescriptive usage of opioids. Drug Alcohol Depend. 2006; 82(2):135–42. pmid:16236466 and Jones CM, Mack KA, Paulozzi LJ. Pharmaceutical overdose deaths, United States, 2010. JAMA. 2013;309:657–659. pmid:23423407).

[11] *Id*.

II. FDA's Abuse-Deterrent Guidance and Framework is Based on Sound Medical, Statistical, and Scientific Principles and was Subject to Public Notice and Comment

FDA developed its 2015 abuse-deterrent framework through a rigorous and robust medical, statistical, and scientific process that was vetted by internal FDA experts and subjected to a significant public notice and comment process, including several public FDA meetings, as the Agency is well aware. The Agency and the public, including PMRS, have had ample opportunity to address any issues or concerns about that framework in those transparent processes.

A. Draft Guidance, Notice and Comment, and Public Meetings

On January 9, 2013, FDA issued its draft AD Guidance, which described how sponsors should study and evaluate abuse-deterrent properties of opioid products, and what claims regarding such properties may be suitable for inclusion in labeling. FDA solicited input and comments from the public on the draft guidance, including specific research topics and types of abuse-deterrent studies. In announcing the draft guidance, FDA explained that "[p]roviding a clear framework for the evaluation and labeling of the abuse-deterrent properties of opioid analgesics intended to deter abuse should help to incentivize the development of safer, less abusable opioid analgesics, and should also facilitate the dissemination of fair and accurate information regarding such products."[12] FDA further emphasized the importance of publishing the draft guidance to "stimulate a productive discussion among FDA, industry, and other stakeholders concerning the appropriate development, evaluation, and labeling of these products." FDA received public comments on its draft guidance from numerous stakeholders, including comments from PMRS.

On August 29, 2014, FDA held individual teleconference calls with the brand and generic drug industries to discuss industry participation in a public meeting to discuss the draft guidance, as well as the overall development and regulation of abuse-deterrent opioid medications.[13] Subsequently, FDA convened a two-day public meeting on October 30 and 31, 2014 to discuss the scientific and technical issues related to the development and in vitro assessment of abuse-deterrent opioids, as well as FDA's approach towards assessing the benefits and risks of all opioid medications, including those with abuse-deterrent properties.[14] The two-day public meeting consisted of extensive presentations regarding abuse-deterrent opioids from various senior FDA officials, members of academia, scientists from pharmaceutical manufacturers, and interested public stakeholders.[15]

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[12] 78 Fed. Reg. 2676 (Jan. 14, 2013), *available at* https://www.gpo.gov/fdsys/pkg/FR-2013-01-14/pdf/2013-00474.pdf.

[13] Transcripts for these meetings are *available at* http://wayback.archive-it.org/7993/20161022055326/http://www.fda.gov/Drugs/NewsEvents/ucm408607.htm.

[14] *See* FDA, Development and Regulation of Abuse-Deterrent Opioid Medications; Public Meeting (hereafter "2014 Public Meeting"), *available at* http://wayback.archive-it.org/7993/20161022055326/http://www.fda.gov/Drugs/NewsEvents/ucm408607.htm.

[15] *See* 2014 Public Meeting Agenda, *available at* http://wayback.archive-it.org/7993/20161023010205/http://www.fda.gov/downloads/Drugs/NewsEvents/UCM420846.pdf.

For example, Janet Woodcock, M.D., Director of FDA's Center for Drug Evaluation and Research (CDER), emphasized that FDA's abuse-deterrent framework "[r]equires clear standards for assessment of formulation performance," including in vitro and abuse liability testing.[16] Similarly, Douglas C. Throckmorton, MD, Deputy Director for Regulatory Programs at CDER, emphasized the need for FDA's abuse-deterrent framework to "[i]ncentivize the development of opioid medications with progressively better abuse-deterrent properties and support their widespread use."[17] Dr. Throckmorton maintained that essential features of abuse-deterrent formulations "can be expected to, or actually do, result in a significant reduction in that product's abuse potential." Mansoor A. Khan, PhD, Director of CDER's Division of Product Quality and Research, outlined FDA's work on manufacturing science and testing of abuse-deterrent formulations, as well as FDA's experience with abuse deterrent submissions and manipulation testing. Dr. Mansoor emphasized the need for abuse-deterrent products to "demonstrate advantages over non-ADF products, both *in vitro* and *in vivo*, by reducing the risk of abuse."[18]

During the public meeting, Dr. Sharon Hertz, Director of FDA's Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) presented FDA's experience with a review of abuse-deterrent products, and noted that FDA was editing the draft guidance based on public comments. She stated that FDA had been taking a "product-by-product approach with the goal to incentivize incremental improvement, ultimately leading to all or most opioid products having abuse-deterrent properties."[19] In addition, Stephen Byrn, PhD, Professor of Medicinal Chemistry at Purdue University, representing the National Institute of Pharmaceutical Technology and Education (NIPTE)--a not-for-profit organization dedicated to fundamental research and education in pharmaceutical product development and manufacturing--presented data and research findings on abuse-deterrent technologies. Dr. Byrn and his colleagues received a grant from FDA to study abuse-deterrent formulations and presented their findings during the two-day meeting, including data on failure modes of oxycodone and oxymorphone products, and excipient properties affecting the mechanical performance of abuse-deterrent formulations.

FDA also received extensive presentations and comments from 14 branded[20] and nine generic[21] drug manufacturers that organized separate working groups to provide comprehensive feedback on FDA's draft AD Guidance and solicitation for comments. Lastly, FDA officials moderated several panels to discuss various topics and questions regarding abuse-deterrent

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[16] *See* 2014 Public Meeting, Dr. Woodcock Presentation at 16, *available at* http://wayback.archive-it.org/7993/20161023010216/http://www.fda.gov/downloads/Drugs/NewsEvents/UCM422373.pdf.
[17] *See* 2014 Public Meeting, Dr. Throckmorton Presentation at 6, *available at* http://wayback.archive-it.org/7993/20161023010217/http://www.fda.gov/downloads/Drugs/NewsEvents/UCM422376.pdf.
[18] *See* 2014 Public Meeting, Dr. Mansoor Presentation at 21, *available at* http://wayback.archive-it.org/7993/20161023010220/http://www.fda.gov/downloads/Drugs/NewsEvents/UCM422379.pdf.
[19] *See* 2014 Public Meeting Summary at 6, *available at* http://wayback.archive-it.org/7993/20161023010215/http://www.fda.gov/downloads/Drugs/NewsEvents/UCM428403.pdf,
[20] The Branded Industry Working Group consisted of: (1) Alkermes; (2) Collegium Pharmaceutical; (3) Egalet Corporation; (4) Endo Pharmaceutical, Inc.; (5) Gruenthal; (6) inSYS Therapeutics, Inc.; (7) KemPharm, Inc.; (8) Mallinckrodt Pharmaceuticals; (9) Pain Therapeutics, Inc.; (10) Pfizer, Inc.; (11) Purdue Pharma L.P.; (12) Reckitt Benckiser; (13) Teva Pharmaceuticals, Ltd.; and (14) Zogenix, Inc.
[21] The Generics Industry Work Group consisted of: (1) Amneal Pharmaceuticals; (2) Kashiv Pharma; (3) Mallinckrodt Pharmaceuticals; (4) Osmotica Pharmaceuticals; (5) Par Pharmaceuticals; (6) Qualitest Pharmaceuticals; (7) Rhodes Pharmaceuticals; (8) Sandoz Pharmaceuticals; and (9) Teva Pharmaceuticals.

opioids (e.g., FDA regulatory oversight, excipients, generics, development and evaluation, benefit/risk assessment, etc.).

B. Final FDA Abuse-Deterrent Guidance

After engaging in this extraordinarily extensive and transparent process for stakeholder input, FDA finalized the AD Guidance in April 2015, incorporating input from the public and numerous experts from academia, industry and related stakeholders who participated in the October 2014 meeting. The final AD Guidance thus represents "FDA's current thinking about the studies that should be conducted to demonstrate that a given formulation has abuse-deterrent properties."[22] The final AD Guidance also "makes recommendations about how those studies should be performed and evaluated, and discusses what labeling claims may be approved based on the results of those studies." Then-FDA-Commissioner Margaret Hamburg, M.D. stated that the final AD Guidance "is a key part of combating opioid abuse," and noted that FDA had "work[ed] hard with industry to support the development of new formulations that are difficult to abuse but are effective and available when needed."[23] Dr. Woodcock emphasized that "[d]evelopment of abuse-deterrent products is a priority for the FDA, and we hope this guidance will lead to more approved drugs with meaningful abuse-deterrent properties."[24] FDA further emphasized in the final AD Guidance that it "considers the development of [abuse-deterrent opioids] a high public health priority."[25]

The AD Guidance explains that abuse-deterrent formulations "should take into consideration the known routes of abuse for the non-abuse-deterrent predecessor or similar products, as well as anticipate the effect that deterring abuse by one route may have on shifting abuse to other, possibly riskier route."[26] FDA categorizes abuse-deterrent formulations as follows: (1) physical (prevent chewing, crushing, cutting, grating, or grinding) and chemical (gelling agents) barriers; (2) agonist/antagonist combinations (e.g., interfere with, reduce, or defeat the euphoria associated with abuse); (3) aversion (adding a substance to produce an unpleasant effect); (4) delivery system; (5) new molecular entities and prodrugs; (6) combinations of two or more of these methods; and (7) other novel approaches or technologies. When designing studies to evaluate the abuse-deterrent characteristics of an opioid, FDA recommends that manufacturers consider "the appropriateness of positive[ ] controls and comparator drugs, outcomes measures, data analyses to permit a meaningful statistical analysis, and selection of subjects for the study."[27]

In evaluating potential abuse-deterrent products, FDA explained that "no absolute magnitude of effect can be set for establishing abuse deterrent characteristics," because FDA

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[22] *See* FDA, Press Release, *FDA issues final guidance on the evaluation and labeling of abuse-deterrent opioids* (Apr. 1, 2015), *available at* https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm440713.htm
[23] *Id*.
[24] *Id*. (also noting that abuse-deterrent formulations "are an important part of the effort to reduce opioid misuse and abuse").
[25] AD Guidance at 2.
[26] AD Guidance at 4.
[27] *Id*. (defining "positive control" 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").

"expects that the market will foster iterative improvements in products."[28] As a result, FDA reasoned that it will "consider the totality of the evidence when reviewing the results of studies evaluating the abuse-deterrent properties of a product," including "abuse-deterrent properties within the context of available therapy" (e.g., "the range of abuse-deterrent and non-abuse-deterrent products on the market at the time of that application").[29]

The AD Guidance outlines three categories of premarket studies, which FDA maintains are necessary to obtain "a full and scientifically rigorous understanding of the impact of a technology or technologies on a product's abuse potential." These include laboratory-based in vitro manipulation and extraction studies (Category 1); pharmacokinetic studies (PK) (Category 2); and clinical abuse potential studies (Category 3). FDA's AD Guidance outlines specific recommendations and considerations for designing and executing each type of study. As described below, Inspirion closely followed FDA's AD Guidance for each type of study. Moreover, Inspirion conferred with FDA throughout the research and development process for RoxyBond to obtain specific guidance on each of its abuse-deterrent studies, and comprehensively incorporated and addressed all of FDA's feedback, a fact that is comprehensively addressed in the NDA record on file with FDA.

III. RoxyBond's Data Fully Satisfied the Standard for FDA Approval and is Consistent with FDA's 2015 Abuse-Deterrent Framework

In April 2017, FDA approved Inspirion's NDA for RoxyBond as the first abuse-deterrent IR, single-entity ("SE") oxycodone hydrochloride ("HCl") tablet intended for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate. In consultation with the FDA's DAAAP, RoxyBond was developed under the 505(b)(2) regulatory pathway using Roxicodone® (NDA 021011; Mallinckrodt, Inc.) as the reference listed drug ("RLD"). FDA supported RoxyBond's approval based on comparable relative bioavailability to Roxicodone, and dose proportionality and food effect studies. Based on these studies, FDA did not require a Phase 3 study.

FDA also based its approval of RoxyBond on in vitro (Category 1) and clinical (Category 2 and 3) abuse-deterrent studies that Inspirion designed in accordance with FDA's AD Guidance. Category 1 testing of RoxyBond included comprehensive evaluation of the effects of physical manipulation, pre-treatment, large volume extraction, syringeability, and small volume extraction. Consistent with FDA's AD Guidance, Inspirion assessed: (1) the ease of extracting the opioid from intact and manipulated product using a variety of commonly available solvents;[30] and (2) the effects of time, temperature (including heat and cold), pH, and agitation on solvent extraction. Inspirion performed these studies through an iterative manner; at multiple time points during the development and the review processes, Inspirion incorporated feedback from FDA to fully characterize RoxyBond's physical and chemical barriers. This included performing all Category 1 testing using the highest 30mg table strength of RoxyBond and Roxicodone for all studies.

[28] *Id*. at 2.
[29] *Id*. at 2-3.
[30] *See id*. at 7. Disclosure of the specific pre-treatments Inspirion used must be kept confidential to prevent potential abusers from obtaining confidential knowledge about RoxyBond's abuse-deterrent properties.

Study O-ARIR-002 was an intranasal human abuse potential ("HAP") study (Category 3) with PK evaluations (Category 2). Study O-ARIR-002 was a randomized, double-blind, double-dummy, placebo-controlled, single-dose, 4-way crossover study. The active treatments in the study were 30mg dosage strengths of RoxyBond or Roxicodone, consistent with FDA's AD Guidance, which recommends using a positive control placebo of an IR formulation of the same opioid.[31] The study enrolled recreational, nondependent opioid users who were experienced with nasal insufflation of opioids, also consistent with FDA's AD Guidance.[32] The primary objective of the study was to determine the abuse potential of manipulated RoxyBond (Tool G) relative to manipulated Roxicodone (Tool E) when administered intranasally to recreational, nondependent opioid users. This objective is consistent with FDA's AD Guidance, which recommends that for products with potential for nasal abuse, "the method that provides the smallest particle size should be used in subsequent studies."[33]

FDA and its relevant Advisory Committees comprehensively reviewed these abuse-deterrent studies and determined that RoxyBond has increased resistance to cutting, crushing, grinding, or breaking using selected tools relative to oxycodone IR tablets. In addition, FDA determined that intact and manipulated RoxyBond tablets resisted extraction in selected household and laboratory solvents under various conditions, including selected pre-treatments. Relative to oxycodone IR tablets, FDA also concluded that RoxyBond's formulation forms a viscous material that resists passage through a needle, which in turn makes it more difficult to administer through intravenous injection. FDA further concluded that, compared to crushed intranasal oxycodone IR tablets, intranasal administration of crushed RoxyBond was associated with statistically significant lower drug liking (Emax) and take drug again (Emax) scores. FDA also found that RoxyBond's data demonstrated physicochemical properties that are expected to reduce abuse by intranasal route of administration.

Dr. Sharon Hertz, Director of FDA's DAAAP, explained at the April 5, 2017 Advisory Committees meeting that FDA did not "have questions about the methods or results of the applicant's studies"[34] and FDA did "not have any disagreements with [Inspirion's] interpretation of the data"[35] for RoxyBond's abuse-deterrent studies. FDA's AADPAC Advisory Committee included the following experts and leaders in pain management treatment and opioid abuse and deterrence research:

1. Raeford E. Brown, Jr., M.D., FAAP, Professor of Anesthesiology and Pediatrics College of Medicine University of Kentucky (AADPAC Chairperson)
2. Brian T. Bateman, M.D., M.Sc., Associate Professor of Anesthesia, Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine; Brigham and Women's Hospital Department of Anesthesia, Critical Care, and Pain Medicine Massachusetts General Hospital

[31] *See* AD Guidance at 11.
[32] *Id*. at 11-12 (recommending that studies be "conducted in opioid-experienced, recreational drug users who have experience with the particular route of abuse being studied, and should generally not be physically dependent or seeking/participating in drug abuse treatment").
[33] *Id*. at 7. Tool G was the only household tool that yielded a consistent output of small particles amenable to intranasal insufflation for both non-pretreated and pretreated RoxyBond.
[34] AdComm Transcript at 175.
[35] *Id*. at 111.

3. Jeffrey L. Galinkin, M.D., FAAP, Professor of Anesthesiology and Pediatrics; Co-Chairman, Colorado Multiple Institutional Review Board, University of Colorado, AMC
4. David S. Craig, Pharm.D., Clinical Pharmacy Specialist, Department of Pharmacy, H. Lee Moffit Cancer Center & Research Institute
5. Anita Gupta, D.O., Pharm.D., Vice Chair and Associate Professor Division of Pain Medicine & Regional Anesthesiology, Department of Anesthesiology, Drexel University College of Medicine
6. Ronald S. Litman, DO, Professor of Anesthesiology & Pediatrics Perelman School of Medicine University of Pennsylvania; Attending Anesthesiologist at The Children's Hospital of Philadelphia; and Medical Director, Institute for Safe Medication Practices
7. Abigail B. Shoben, PhD, Associate Professor, Division of Biostatistics, College of Public Health, The Ohio State University
8. Mary Ellen McCann, M.D., M.P.H., Associate Professor of Anesthesia, Harvard Medical School, Senior Associate in Anesthesia Boston Children's Hospital
9. Kevin L. Zacharoff, M.D., FACIP, FACPE, FAAP, Faculty and Clinical Instructor, Pain and Medical Ethics, State University of New York, Stony Brook School of Medicine; Ethics Committee Chair, St. Catherine of Siena Medical Center

FDA's DSaRM Advisory Committee included the following experts and leaders in pain management treatment and opioid abuse and deterrence research:

10. Niteesh K. Choudhry, M.D., PhD, Professor, Harvard Medical School; Associate Physician, Brigham and Women's Hospital
11. Christopher H. Schmid, PhD, Professor of Biostatistics, Center for Evidence Based Medicine, Department of Biostatistics, Brown University School of Public Health
12. Terri L. Warholak, PhD, RPh, FAPhA, Assistant Professor, Division of Health Promotion Sciences, College of Public Health; Adjunct Clinical Instructor, College of Nursing; Associate Professor with Tenure, Department of Pharmacy Practice and Science, College of Pharmacy, University of Arizona
13. Gregory E. Amidon, PhD, Research Professor of Pharmaceutical Sciences, College of Pharmacy, Department of Pharmaceutical Sciences, University of Michigan
14. Alan D. Kaye, MD, PhD, Professor and Chairman, Department of Anesthesia, Louisiana State University School of Medicine
15. Charles W. Emala, Sr., MS, M.D., Professor and Vice-Chair for Research Department of Anesthesiology, Columbia University College of Physicians & Surgeons
16. Arthur H. Kibbe, RPh, PhD, Retired Professor of Pharmaceutical Sciences, Nesbitt School of Pharmacy, Wilkes University
17. Elaine H. Morrato, DrPH, MPH, Associate Dean for Public Health Practice, Associate Professor Department of Health Systems, Management and Policy, Colorado School of Public Health, University of Colorado Anschutz Medical Campus
18. Sharon L. Walsh, PhD, Professor of Behavioral Science, Psychiatry, Pharmacology and Pharmaceutical Sciences Director, Center on Drug and Alcohol Research, University of Kentucky[36]

[36] *See* AdComm Meeting Roster, *available at* https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM551775.pdf.

Although the PMRS Petition purports to second guess this array of eminent experts, the Advisory Committees in fact voted 19 to 1 in favor of approving RoxyBond as an abuse-deterrent product by the nasal route of abuse. The Advisory Committees Summary Minutes reflect that committee members "stated that, on the whole, the pharmacokinetic and pharmacodynamic data provided were compelling and showed that the product will make it more difficult for some people to abuse it."[37] The Advisory Committees further voted 16 to 4 in favor of labeling RoxyBond as abuse-deterrent by the intravenous route, with committee members finding that the "in vitro data, drug dissolution data, gelling properties of the product, and large injection volume necessary were convincing factors in their vote."[38]

A. FDA Determined that the RoxyBond Particle Size Manipulation and Extraction Studies Were Appropriate and Consistent with FDA Guidance

The Advisory Committees findings reflect that the manipulation studies performed by Inspirion supported that RoxyBond tablets were resistant to manipulation through crushing, grinding, or otherwise extracting oxycodone from the tablet. Importantly for purposes of the Petition, FDA also found that the particle size manipulation studies were conducted in a manner fully consistent with FDA's AD Guidance. Specifically, FDA concluded that physical manipulation using "most of the tools tested are difficult to impractical to particle size reduce the RoxyBond."[39] FDA also found that RoxyBond tablets were harder and comparatively more difficult to be crushed or ground into a fine insufflatable powder than Roxicodone when using Tool E.[40]

FDA also noted that the extraction studies for RoxyBond tablets showed a "big contrast" as compared to Roxicodone tablets.[41] Specifically, FDA concluded that intact and manipulated RoxyBond tablets resisted extraction in selected household and laboratory solvents under various conditions, including selected pre-treatments.

A conclusive majority of members of the FDA Advisory Committees confirmed that the RoxyBond particle size manipulation and extraction studies demonstrated nasal-abuse deterrence and were consistent with FDA's AD Guidance. For example, Dr. Walsh concluded that RoxyBond's data, "in comparison to other[ER products] that are already approved" with nasal abuse-deterrence labeling, "met the letter of the law."[42] Dr. McCann explained that he was "convinced that [RoxyBond] is a nasal deterrent with the data that's been presented."[43] Dr. Kibbe emphasized that RoxyBond's data showed that it would "deter [abuse]" and "make[] it

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[37] *See* AdComm Summary Minutes at 5, *available at* https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM556517.pdf. The only committee member who voted "No" stated that "the definition of abuse deterrence was unclear."
[38] *Id*. at 6.
[39] FDA, FDA Briefing Document: 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) at 97 (hereafter "FDA Briefing Document).
[40] *Id*.
[41] *Id*. at 102.
[42] AdComm Transcript at 195.
[43] *Id*. at 197.

more difficult" to get the most oxycodone out of it.[44] He further maintained that RoxyBond was "better than the current product in terms of making it more difficult" to abuse, and that if the target for abuse deterrence "is really the casual and first-time user, [RoxyBond] … won."[45] Dr. Kibbe concluded that RoxyBond's "polymers make it really difficult for you to get a full dose intranasally and make it really difficult to directly get an injectable."[46]

Dr. Bateman reasoned that RoxyBond's manipulation data showed that "with most tools, it's hard to generate a large volume of fine powder [] compared to Roxicodone" and that "most of the tools had quite low yields of fine particles."[47] Dr. Bateman further emphasized that RoxyBond "represents a really important advance as the first immediate-release opioid with properties intended to deter abuse," and that it provides a "barrier to abuse by intravenous and intranasal routes," which "meets an important public health need."[48] Dr. Shoben agreed with and affirmed Dr. Bateman's comments.[49] These conclusions are consistent with FDA's AD Guidance, which recommends that sponsors assess abuse-deterrent products using various "simple and sophisticated mechanical and chemical ways of manipulation," such as readily available items such as spoons, cutters, and coffee grinders.[50]

Dr. Choudhry explained that the "amount of oxycodone that's recovered [from RoxyBond] is compellingly smaller" than Roxicodone.[51] Thus, he concluded that, "at least on the nasal route, in addition to the idea of the PK studies … and the liking studies …, [RoxyBond's abuse-deterrent properties are] fairly convincing to me, both in terms of direction, effect, and consistency."[52] Dr. Zacharoff voted in favor of the nasal abuse-deterrent labeling after finding that Inspirion "did what was requested of them as per the [AD] guidance."[53] Dr. Galinkin also voted in favor of the nasal abuse-deterrent labeling after finding the PK and likeability data "very persuasive."[54]

Overall, both FDA and the leading scientists and physicians in the field found that the data supporting RoxyBond with respect to manipulation and extraction were both consistent with FDA's AD Guidance and scientifically compelling. Nothing in the PMRS Petition undermines those conclusions.

B. **FDA Determined that the RoxyBond Syringeability Studies were Appropriate and Consistent with FDA Guidance**

FDA concluded that the syringeability studies showed that powder from manipulated RoxyBond tablets (particle size reduced using Tool C or Tool G) "formed a material that was

[44] AdComm Transcript at 200.
[45] *Id*.
[46] *Id*. at 201.
[47] *Id*.
[48] *Id*. at 233.
[49] *Id*.
[50] AD Guidance at 6.
[51] AdComm Transcript at 203.
[52] *Id*. at 204.
[53] *Id*. at 211.
[54] *Id*.

difficult to syringe and only produced a small amount of injectable liquid."[55] The recoveries ranged from 2.5 to 18.9% even with Needle Gauge C when prepared using both Volume A and Volume B of Solvent A extracted up to 30 minutes (consistent with FDA's AD Guidance).[56] FDA also determined that it was more difficult to syringe RoxyBond samples when doubling the number of tablets per sample compared to Roxicodone, and the recoveries were even lower than a single tablet sample.

Similar to the particle size manipulation and extraction studies, numerous members of the FDA Advisory Committees found that RoxyBond's data demonstrated abuse-deterrence for intravenous (IV) use. For example, Dr. Choudhry emphasized that the intravenous abuse data was "even more convincing" because "it's not possible to really syringe [RoxyBond] in any meaningful way."[57] He maintained that the syringeability data was in the "2 to 5 to 6 percentage point range out of a possible 100, which [showed] that [RoxyBond] meets the standard of abuse-deterrent."[58] Accordingly, Dr. Choudhry voted in favor of the IV abuse-deterrent labeling, reasoning that the data presented "in terms of recoverability in solution and the gelling formulations [were] compelling."[59]

Dr. Galinkin voted in favor of the IV abuse-deterrent labeling, reasoning that the "syringeability was much more difficult" and because "much larger volumes were required in order to get [RoxyBond] into a form which could actually syringe," both of which were "important features."[60] Dr. Brown voted in favor of the IV abuse-deterrent labeling, reasoning that RoxyBond's "multistep process will prevent many" "early users of drugs like this" "from going on to this mechanism of abuse."[61] Dr. Craig voted in favor of the IV abuse-deterrent labeling, reasoning that the "inability to syringe the product" after grinding it was "convincing."[62] Again, the data supporting RoxyBond with respect to syringeability were found -- without reservation -- to be both consistent with FDA's AD Guidance and scientifically compelling, and no data or other information in the PMRS Petition alter those conclusions.

C. FDA Determined that the HAP ("Liking") Studies were Appropriate and Consistent with FDA Guidance

FDA concluded that the HAP Studies were appropriate and consistent with FDA's AD Guidance, and that, when compared to crushed intranasal oxycodone IR tablets, intranasal administration of crushed RoxyBond was associated with statistically significant lower drug liking (Emax) and take drug again (Emax) scores.[63] FDA determined that the four subjective

[55] FDA Briefing Document at 103.
[56] *See* AD Guidance at 7 (explaining that products with potential for intravenous abuse should be tested with extraction times between 30 seconds to 30 minutes).
[57] AdComm Transcript at 204.
[58] *Id*.
[59] *Id*. at 217
[60] *Id*.
[61] *Id*. at 219.
[62] *Id*.
[63] *See e.g.* AD Guidance at 12 (explaining that for Category 3 studies using the intranasal route of administration, "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").

measures used in O-ARIR-002 were validated because the statistical analyses demonstrated that the maximum responses (Emax) produced by intranasal crushed Roxicodone 30 mg (positive control) was significantly ($p<0.0001$) greater than that produced by placebo.[64]

Various members of the FDA Advisory Committees also emphasized that the RoxyBond liking studies supported abuse-deterrent labeling. For example, Dr. Emala noted that the drug liking measures for RoxyBond "f[e]ll well within the range of the extended-release products for drug liking, Emax high, take-drug-again scores" for the ER products that currently carry nasal abuse-deterrent labeling.[65] Dr. Morrato concluded that the "drug-liking abuse potential studies, and particularly [] the direction and magnitude of the effects were comparable to drugs that have been approved with similar" nasal abuse deterrent labeling.[66]

As in other areas, the review of the RoxyBond HAP studies met all FDA requirements and the Advisory Committees concurred. Nothing in the PMRS Petition undermines FDA's conclusions from that rigorous review process.

IV. FDA Should Deny the Petition Because it Does Not Meet the Applicable Standards or Grounds for Such Agency Action

FDA should deny the PMRS Petition because FDA correctly and reasonably approved RoxyBond and its labeling under applicable statutory and regulatory standards for drug approval. The FDA properly based its decision on robust scientific and clinical data consistent with FDA's abuse-deterrent framework, and the PMRS Petition does not otherwise meet the applicable standards or grounds under 21 C.F.R. § 10.35(e). FDA regulations direct the Commissioner to grant a petition to stay only if all four of the following factors are met: (1) the delay resulting from the stay is not outweighed by public health or other public interests; (2) the petitioner has demonstrated sound public policy grounds supporting the stay; (3) the petitioner's case is not frivolous and is being pursued in good faith; and (4) the petitioner will suffer irreparable injury.[67] The PMRS Petition does not satisfy any individual factor, let alone all four factors as required. Therefore, the Petition's unprecedented request that FDA stay the RoxyBond approval should be denied.

First, not only would a stay of RoxyBond's approval not protect the public health or public interest, it would actually cause harm to the public health and well-being. For the reasons explained above, such an action would deny patients access to the first FDA-approved abuse-deterrent IR opioid. While RoxyBond is not presently on the market, DSI is working diligently to commercialize it. Once it is marketed, it will help to fill a critical unmet medical need for abuse-deterrent IR opioids, which account for over 90% of the opioid prescriptions dispensed. And, opioid abuse rates were markedly higher for IR than ER medications. As Dr. Gottlieb has observed, IR opioids "serve as a gateway" for abuse of ER products. Thus, staying RoxyBond's approval would deny the millions of patients in need of appropriate pain management therapy access to the first abuse-deterrent IR product.

[64] FDA Briefing Document at 107.
[65] AdComm Transcript at 193-94.
[66] *Id*. at 210-11.
[67] *See* 21 C.F.R. § 10.35(e).

Staying RoxyBond's approval would also negate the thorough and careful review conducted by the FDA and its Advisory Committees. Consistent with the AD Guidance, FDA's review carefully considered the RoxyBond abuse-deterrent studies and properties, including the review conducted by FDA's Advisory Committees, and approved RoxyBond "within the context" of there being no abuse-deterrent IR opioid. Thus, RoxyBond's approval is consistent with FDA's goal of the AD Guidance--to provide a "clear framework for the evaluation and labeling of the abuse-deterrent properties," and to lead to "more approved drugs with meaningful abuse-deterrent properties." The approval is also consistent with FDA's policy goal of making abuse-deterrent opioids a "high public health priority."

Second, PMRS has not demonstrated any sound public policy grounds for supporting the Petition because, as noted above, FDA's AD Guidance is based on sound medical, statistical, and scientific principles founded in robust, peer-reviewed scientific and medical literature. The AD Guidance was subject to notice and comment, and FDA held various public meetings and listened to numerous stakeholders in developing the framework. Inspirion developed RoxyBond's abuse-deterrent studies under FDA's framework in direct consultation with the Agency to ensure that RoxyBond complied with FDA's AD Guidance. FDA approved RoxyBond based on robust scientific and clinical data from these abuse-deterrent studies.

As courts have recognized, "[t]he public has an interest in federal agency compliance with its governing statute," and here, FDA complied with such governing statutes when approving RoxyBond.[68] Conversely, PMRS has not offered any evidence as to why FDA's approval of RoxyBond conflicts with public policy. To the contrary, FDA's approval of RoxyBond followed all applicable FDA laws, regulations, and guidance in a manner consistent with FDA's public policy for abuse-deterrent opioids. Moreover, to change the framework now -- after a drug has been approved -- would discourage would-be innovators who are seeking to meet important and unmet medical needs (particularly in an opioid crisis) based on reliance on FDA published rules and guidance. It is important as a matter of policy that innovators have assurance that FDA policy documents can be relied upon.

Third, the PMRS petition appears to be driven by financial interests rather than good faith public health concerns. PMRS acknowledges in its May 2017 Petition, as it must, that it has developed an IR abuse-deterrent opioid for FDA approval. However, no further information about this product is publicly available. PMRS does have several patents related to abuse-deterrent opioids, including an IR opioid.[69] In addition, PMRS admits in its February 19, 2016 Citizen's Petition that it "is the commercial manufacturer of Opana® (oxymorphone HCl) tablets."[70] PMRS actions indicate that their interest in this area -- and the burden it has placed on FDA by filing numerous petitions -- is likely driven by a desire to see FDA guidance favor its proprietary -- yet undisclosed and unproven -- technology, to the detriment of the public health.

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[68] *Bayer HealthCare, LLC v. U.S. Food & Drug Admin*., 942 F. Supp. 2d 17, 27 (D.D.C. 2013).

[69] *See e.g.*, Patent Nos. 9707184 (immediate release abuse deterrent liquid fill dosage form); 20170020822 (extended release abuse deterrent liquid fill dosage form); 20160015650 (immediate release abuse deterrent liquid fill dosage form); and 20170007544 (extruded extended release abuse deterrent pill).

[70] *See* PMRS Citizen's Petition at 21 (Feb. 19, 2016). Opana® immediate release tablets are not an abuse-deterrent product.

PMRS has failed to provide any valid scientific evidence to dispute FDA's comprehensive review and approval of RoxyBond, which the agency based on extensive scientific and clinical data that showed RoxyBond's abuse-deterrent attributes, consistent with the AD Guidance. FDA's AD Guidance did not preclude PMRS from filing an NDA or receiving the same advice and consultation from FDA that Inspirion utilized. PMRS just failed to do so before FDA approved RoxyBond. And, PMRS failed to explain or even acknowledge how or whether its own IR product would be comparable or superior to RoxyBond--if FDA would actually approve it. Instead, the PMRS petition is merely an attempt to prevent the first abuse-deterrent IR opioid from being made available to patients, regardless of the public health consequences.

Finally, FDA should deny the PMRS petition because PMRS will not suffer any irreparable injury. FDA approved RoxyBond based on robust scientific and clinical data that is in accordance with FDA approval standards and consistent with FDA's AD Guidance. There is no harm or injury to PMRS because FDA properly studied and approved RoxyBond, and thus, any future PMRS product will not be held to an inappropriate approval standard. Further, the fact that PMRS's future product may not be eligible for priority review does not constitute irreparable harm, as FDA's approval of RoxyBond was consistent with applicable laws and regulations. Nothing prevented PMRS from filing its NDA before RoxyBond, and failing to reach the market before a competitor does not constitute any form of injury or harm. Accordingly, FDA should reject the PMRS Petition because it fails to satisfy each of the factors of 21 C.F.R. § 10.35(e).

While the PMRS Petition asks FDA to stay the date of RoxyBond's approval, FDA lacks the authority under the Federal, Food, Drug, and Cosmetic Act (FDCA) to delay the effective date of a drug that the agency has already approved. Rather, FDA would need to notify Inspirion of its proposal to withdraw approval of the RoxyBond NDA. Under 21 C.F.R. § 314.150, FDA may propose to withdraw an NDA only if the following apply: (1) the Secretary of the U.S. Department of Health and Human Services (HHS) has suspended the approval of a new drug on a finding that there is an imminent hazard to public health; or (2) FDA finds that: (i) clinical or other experience, tests, or other scientific data show that the drug is unsafe for use; (ii) new evidence of clinical experience or tests by new methods, not contained in the application or not available to FDA until after the application was approved, reveal that the drug is not shown to be safe for use; (iii) new information before FDA shows there is a lack of substantial evidence from adequate and well-controlled investigations; or (iv) the application contains an untrue statement of a material fact. Neither PMRS's Petition nor any other available data or evidence satisfies any one of these conditions.

First, the Secretary of HHS clearly cannot suspend RoxyBond's approval based on any imminent hazard to public health. To the contrary, the Secretary of HHS and the President are in the process of declaring the opioid abuse epidemic a national emergency. And, as noted above, Dr. Gottlieb has emphasized the importance of approving abuse-deterrent IR opioids as a critical tool to fight the epidemic. Second, the PMRS petition contains no scientific, clinical, or other evidence to demonstrate that RoxyBond is unsafe for use. To the contrary, both FDA and the FDA Advisory Committees conclusively determined RoxyBond to be safe, effective, and abuse-deterrent in accordance with approved labeling, as described in detail above. RoxyBond's

approval will help protect public health by providing patients and prescribers access to the first abuse-deterrent IR opioid that is also an effective pain management therapy. In sum, nothing has changed since FDA and the Advisory Committees' careful and comprehensive review of the RoxyBond NDA that would negate FDA's approval decision. We are not aware of any new information submitted by PMRS or otherwise before FDA to suggest that there is a lack of scientific support for RoxyBond's approval and labeling.[71]

* * *

FDA approved RoxyBond based on extensive and well-conducted studies, which demonstrated that RoxyBond is abuse-deterrent to certain forms of manipulation. Inspirion designed and executed the RoxyBond abuse-deterrent studies in compliance with FDA advice and consistent with FDA's AD Guidance. RoxyBond's approval as the first abuse-deterrent IR opioid is critical to helping address the opioid abuse epidemic and filling a significant unmet need, given that 90% of opioids prescribed are IR products. RoxyBond's approval is also consistent with Dr. Gottlieb's goals to "reduc[e] the rate of new addictions" by approving abuse-deterrent IR opioids. In contrast, PMRS has failed to offer any scientific, clinical, or other evidence to support its Petition to stay RoxyBond's approval. Instead, the PMRS Petition would only harm the public health by preventing patients access to the first abuse-deterrent IR opioid and calling into question FDA's scientifically rigorous approval process. Accordingly, we respectfully request that FDA deny the PMRS Petition for Stay of Action in full and without delay.

Respectfully submitted,

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Senior Vice President, General Counsel & Secretary

cc: Carol J. Bennet
Deputy Director, Office of Regulatory Policy
Center for Drug Evaluation and Research
Food and Drug Administration

[71] In addition, there is no evidence whatsoever that Inspirion's NDA contained an untrue statement of material fact.