IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF PENNSYLVANIA

PHARMACEUTICAL MANUFACTURING RESEARCH SERVICES, INC., Plaintiff-Petitioner, v. UNITED STATES FOOD AND DRUG ADMINISTRATION, SCOTT GOTTLIEB, M.D., in his official capacity as the Commissioner of Food and Drugs, and his successors and assigns, and ERIC D. HARGAN, in his official capacity as the Acting Secretary of the United States Department of Health and Human Services, as well as his successors and assigns, Defendants.	**Civil Action No. 2:17-cv-4898-GJP**

ORDER

AND NOW, this _____ day of _____, 2018, upon consideration of Plaintiff, Pharmaceutical Manufacturing Research Services, Inc.'s Motion for Summary Judgment, and any response thereto, it is hereby **ORDERED** that said Motion is granted pursuant to Federal Rule of Civil Procedure 56, and judgment is entered in favor of Plaintiff, Pharmaceutical Manufacturing Research Services, Inc., and against Defendants, United States Food and Drug Administration, Scott Gottlieb, M.D., and Eric D. Hargan;

IT IS FURTHER ORDERED that the denial of Plaintiff's Petition for Stay of Action was arbitrary, capricious, an abuse of discretion, and not in accordance with law, and in excess of statutory jurisdiction, authority, and limitations within the meaning of 5 U.S.C. § 706(2)(A) and (C);

IT IS FURTHER ORDERED that FDA's decision to deny Plaintiff's Petition for Stay of Action is reversed, vacated and remanded to FDA for further action consistent with this Order and in a manner that addresses the abuse deterrent and chronic use issues set forth in Plaintiff's Amended Complaint; and

IT IS FURTHER ORDERED Plaintiff's application for injunctive relief is granted and the effective date of Inspirion Delivery Services, LLC's New Drug Application 209777 for ROXYBOND is stayed pending disposition of Plaintiff's Petition for Stay of Action and pending citizens petitions.

BY THE COURT:

_____

Honorable Gerald J. Pappert, J.

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PHARMACEUTICAL MANUFACTURING RESEARCH SERVICES, INC., Plaintiff-Petitioner, v. UNITED STATES FOOD AND DRUG ADMINISTRATION, SCOTT GOTTLIEB, M.D., in his official capacity as the Commissioner of Food and Drugs, and his successors and assigns, and ERIC D. HARGAN, in his official capacity as the Acting Secretary of the United States Department of Health and Human Services, as well as his successors and assigns, Defendants.	**Civil Action No. 2:17-cv-4898-GJP** **NOTICE OF PLAINTIFF'S MOTION FOR SUMMARY JUDGMENT PURSUANT TO FEDERAL RULE OF CIVIL PROCEDURE 56**

COUNSEL:

PLEASE TAKE NOTICE that as soon as counsel may be heard, Plaintiff Pharmaceutical Manufacturing Research Services, Inc. shall apply to the United States District Court for entry of an Order granting summary judgment in favor of Plaintiff; and

PLEASE TAKE FURTHER NOTICE that Plaintiff is moving pursuant to the Court's scheduling Order dated May 18, 2018 [Doc. 31] and in accordance with that Order, FDA's opposition and cross-motion, if any, is due on or before August 1, 2018;

PLEASE TAKE FURTHER NOTICE that oral argument is requested on a date to be set by this Court; and

PLEASE TAKE FURTHER NOTICE that, in support of the motion, we shall rely upon the Memorandum of Law in Support of Plaintiff's Motion for Summary Judgment, with an Index and Exhibits, and Statement of Undisputed Material Facts submitted herewith; and

PLEASE TAKE FURTHER NOTICE that a proposed form of Order is submitted with this motion.

McCARTER & ENGLISH, LLP
Attorneys for Plaintiff,
Pharmaceutical Manufacturing Research Services, Inc.

By: *s/Natalie S. Watson*
Natalie S. Watson
Member of the Firm

Dated: July 2, 2018

IN THE UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF PENNSYLVANIA

PHARMACEUTICAL MANUFACTURING RESEARCH SERVICES, INC., Plaintiff-Petitioner, v. UNITED STATES FOOD AND DRUG ADMINISTRATION, SCOTT GOTTLIEB, M.D., in his official capacity as the Commissioner of Food and Drugs, and his successors and assigns, and ERIC D. HARGAN, in his official capacity as the Acting Secretary of the United States Department of Health and Human Services, as well as his successors and assigns, Defendants.	**Civil Action No. 2:17-cv-4898-GJP**

MEMORANDUM OF LAW IN SUPPORT OF PLAINTIFF PHARMACEUTICAL MANUFACTURING RESEARCH SERVICES INC.'S MOTION FOR SUMMARY JUDGMENT

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PRELIMINARY STATEMENT

Plaintiff, Pharmaceutical Manufacturing Research Services ("PMRS"), respectfully submits this Memorandum of Law in Support of its Motion for Summary Judgment pursuant to Federal Rule of Civil Procedure 56. This action seeks to vacate the Food and Drug Administration's ("FDA's") October 19, 2017, denial of PMRS's Petition for Stay of Action ("PSA" or "Petition"), a Petition that raises pressing public health issues. PMRS's PSA sought to stay the effective date of FDA's approval of Inspirion Delivery Services, LLC's New Drug Application 209777 for a product known as ROXYBOND (oxycodone hydrochloride) tablets, ("ROXYBOND" or "Inspirion NDA"), pending FDA's substantive responses to two pending Citizen Petitions previously submitted by PMRS before FDA's approval of ROXYBOND and pending FDA's substantive responses to certain stand-alone issues raised in PMRS's PSA pertaining specifically to ROXYBOND approval. For the reasons set forth below, PMRS's motion for summary judgment must be granted and an order for declaratory and injunctive relief must issue due to Defendants' violation of: Federal Food, Drug, and Cosmetic Act ("FDCA"), 21 U.S.C. § 301, *et seq.*; Food and Drug Administration's ("FDA's") regulations and policies implementing the FDCA; and the Administrative Procedure Act ("APA"), 5 U.S.C. § 706.

As discussed in detail below, FDA's approval of opioid drugs as a class for treatment of chronic pain fails to give effect to the unambiguously expressed intent of Congress in enacting and amending the Federal Food Drug and Cosmetic Act, 21 U.S.C. § 301 *et seq.* (the "Act"), 21 U.S.C. § 301 *et seq.* In the past two years, it has come to light that FDA has been approving opioid drug products for treatment of chronic pain despite a lack of substantial evidence, as is required by 21 U.S.C. § 355(b), to support the efficacy of those products in a chronic use setting. Rather than addressing their improper approval processes for opioids with labeling for the

treatment of chronic pain, FDA instead has pursued abuse deterrent formulation and labeling, a Band-Aid approach that has done nothing to slow the destruction caused by the opioid crisis.

Through its pending Citizen Petitions, PMRS made recommendations to remedy FDA's flawed approval process for opioids labeled for chronic use and abuse deterrence. FDA expressly acknowledged the importance of the issues raised in those Citizen Petitions. Regrettably, though, FDA still is pushing forward with its "fire, aim, ready" approach to the approval of opioids with such labeling by approving yet another opioid analgesic with labeling for chronic pain and abuse deterrence, ROXYBOND.

PMRS responded by filing its PSA, seeking to stay the effective approval date of ROXYBOND pending FDA's completion of its review of the important issues and recommendations set forth in PMRS's pending Citizen Petitions and also the substantive issues raised in its PSA. Yet despite recognizing the significant public health issues raised in PMRS's Citizen Petitions and PSA, FDA denied PMRS's PSA. The uncontroverted record confirms that in denying PMRS's PSA, FDA refused or otherwise failed to consider the documented statutory and regulatory failures of its approval of opioids for use in the treatment of chronic pain, even though FDA is obligated to consider substantial evidence of efficacy as a threshold matter. FDA has an independent duty analyze safety and efficacy for all new drug applications. Those obligations are at the core of our PSA. Failing to consider such threshold statutory compliance issues in PMRS's PSA was arbitrary and capricious.

PMRS's PSA requests narrow relief. Specifically, PMRS sought to stay the effective approval date of ROXYBOND so that FDA can consider PMRS's pending Citizen Petitions – and the solutions set forth in them – before unleashing yet another opioid into the market. FDA's refusal to grant the stay meets the requirements of the Administrative Procedure Act

("APA"), 5 U.S.C. § 706. In turn, FDA's denial of PMRS's PSA must be reversed and the relief sought in PMRS's PSA must be granted.

PROCEDURAL HISTORY AND STATEMENT OF UNCONTESTED MATERIAL FACTS

PMRS respectfully adopts by reference as if set forth fully herein PMRS's Rule 56.1 Statement of Uncontested Material Facts.

ARGUMENT

I. LEGAL STANDARD

A. Standard Applicable on Motion for Summary Judgment.

Summary judgment is proper where, as here, "the pleadings, the discovery and disclosure materials on file, and any affidavits show that there is no genuine issue as to any material fact and that the movant is entitled to judgment as a matter of law." Fed. R. Civ. P. 56(c)(2); *accord Celotex Corp. v. Catrett*, 477 U.S. 317, 322 (1986); *Willis v. UPMC Children's Hosp. of Pittsburgh*, 808 F.3d 638, 643 (3d Cir. 2015). Defendants cannot avoid summary judgment by relying upon unsupported assertions or speculation. *See Groman v. Twp. of Manalapan*, 47 F.3d 628, 637 (3d Cir. 1995). Instead, defendants must present evidence of a genuine factual issue, *Celotex*, *supra*, 477 U.S. at 324, and that there is more than just "some metaphysical doubt as to the material facts." *Matsushita Elec. Indus. Co., Ltd. v. Zenith Radio Corp.*, 475 U.S. 574, 586-87 (1986). Here, the uncontroverted facts demonstrate that FDA's decision to deny PMRS' PSA was arbitrary and capricious as a matter of law. As such, summary judgment should be entered in favor of PMRS.

B. Standard Applicable to Petitions for Relief Filed Under the Administrative Procedure Act, 5 U.S.C. § 701, *et seq*.

This matter concerns FDA's fatally flawed analysis and wrongful decision to deny PMRS's May 11, 2017, Petition for Stay of Action ("PSA"). Decisions of administrative

agencies such as the FDA are subject to judicial review by a District Court pursuant to the Administrative Procedure Act ("APA"), 5 U.S.C. § 701, *et seq.; see Abbott Labs. v. Gardner,* 387 U.S. 136, 140–41, 87 S.Ct. 1507, 18 L.Ed.2d 681 (1967). Pursuant to Section 706:

> the reviewing court shall decide all relevant questions of law, interpret constitutional and statutory provisions, and determine the meaning or applicability of the terms of an agency action. The reviewing court shall (2) hold unlawful and set aside agency action, findings, and conclusions found to be (A) arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law… [or] (C) in excess of statutory jurisdiction, authority, or limitations, or short of statutory right.
>
> An agency action is arbitrary or capricious:
>
> if the agency has relied on factors which Congress has not intended it to consider, entirely failed to consider an important aspect of the problem, offered an explanation for its decision that runs counter to the evidence before the agency, or is so implausible that it could not be ascribed to a difference in view or the product of agency expertise.

Motor Vehicle Mfrs. Ass'n of U.S. v. State Farm Mut. Auto. Ins. Co., 463 U.S. 29, 43 (1983).

On a motion for relief under Section 706 of the APA, the Court, giving deference to the agency, must determine whether the agency acted in an arbitrary or capricious manner and "must consider whether the [agency's] decision was based on a consideration of the relevant factors and whether there has been a clear error of judgment." *Marsh v. Or. Natural Res. Council*, 490 U.S. 360, 378 (1989) (quotation marks omitted). Furthermore, "the agency must examine the relevant data and articulate a satisfactory explanation for its action including a 'rational connection between the facts found and the choice made.'" *Motor Vehicle Mfrs. Ass'n of U.S., Inc.*, 463 U.S. at 43 (quoting *Burlington Truck Lines, Inc. v. United States*, 371 U.S. 156, 168 (1962)).

As discussed in detail below, FDA has failed to give effect to the unambiguously expressed intent of Congress in enacting and amending the Federal Food Drug and Cosmetic Act, 21 U.S.C. § 301 *et seq.* (the "Act"), 21 U.S.C. § 301 *et seq.* Specifically, in denying PMRS's PSA, FDA failed to comport with the requirement that a drug not be approved unless

there is proof that in addition to being "safe for use," that drug is "effective in use." 21 U.S.C. § 355(b). In the past years, it has come to light that FDA's current methodology for approval of so-called abuse deterrent labeling for opioids does not satisfy the requisite statutory standard, is scientifically flawed, and results in false and misleading labeling. Such labeling gives a false sense of security as to any meaningful solution to the raging opioid epidemic.

Rather than addressing improper approval processes for opioids with labeling for treatment of chronic pain, FDA pursued abuse deterrent formulation and labeling, an approach that has done nothing but fuel the opioid crisis. FDA's refusal to consider its failings under 21 U.S.C. § 355(b) with respect to opioids – information at the core of PMRS's Citizen Petitions and PSA – was arbitrary and capricious and must be overturned for the reasons set forth below.

II. FDA'S DENIAL OF PMRS'S PSA WAS ARBITRARY AND CAPRICIOUS BECAUSE FDA DID NOT CONSIDER ITS FAILURE TO COMPLY WITH OPERATIVE STATUTORY AND REGULATORY OBLIGATIONS IN APPROVING OPIOIDS FOR CHRONIC USE AND WITH ABUSE DETERRENT LABELING.

As the uncontroverted record confirms, FDA did not consider its failure to comply with its statutory and regulatory obligations in approving opioids with labeling for chronic use in connection with its denial of PMRS's PSA. As such, FDA's denial of PMRS's PSA was arbitrary and capricious and must be reversed.

A. By Statute, Drug Applicants Must Provide Substantial Evidence of Efficacy for the Conditions of Use Approved.

In 1962, Congress amended the Federal Food, Drug, and Cosmetic Act (FDCA) to require proof that a drug product is "effective in use," in addition to being "safe for use." 21 U.S.C. § 355(b). Thus, to obtain market approval, a drug manufacturer is required to establish by "substantial evidence" that a new drug "will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed

labeling." 21 U.S.C. § 355(d). Reports of adequate and well-controlled investigations provide the primary basis for FDA's determination of whether there is "substantial evidence" to support the claims of effectiveness for new drugs. 21 C.F.R. 314.126(a). FDA considers certain characteristics in determining whether an investigation is adequate and well-controlled, including whether the study is placebo-controlled. 21 C.F.R. 314.126(b).

The 1962 amendment to the FDCA also required FDA to conduct a retrospective evaluation of the effectiveness of the drug products that FDA had approved as safe between 1938 and 1962 through the new drug approval process. FDA contracted with the National Academy of Sciences-National Research Council (NAS-NRC) to create expert panels to review by class the efficacy of each approved drug. The NAS/NRC reports for these drug products were submitted to FDA in the late 1960s and early 1970s. FDA's administrative implementation of the NAS/NRC reports was called the Drug Efficacy Study Implementation (DESI).

B. The 505(b)(2) Regulatory Pathway of the FDCA

Section 505 of the FD&C Act describes, as relevant here, two types of new drug applications: (1) an application that contains full reports of investigations of safety and effectiveness (section 505(b)(1)); and (2) an application that contains **full reports of investigations of safety and effectiveness** but where at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference (section 505(b)(2)). ROXYBOND was submitted as a 505(b)(2) application with reference to the Agency's prior findings of safety and efficacy for ROXICODONE (i.e., the "reference product" for ROXYBOND). Exhibit Q, *Summary Review (NDA 20977)*, at 2 (page 3 of the document), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/209777Orig1s000SumR.pdf (last visited Jun. 30, 2018). ROXYBOND did "not conduct[] any additional efficacy or safety

studies." *Id*. at 3-4. **Thus, to be in compliance with the FDCA, ROXYBOND's approval must have relied on FDA's prior determination of the safety and effectiveness of its reference product, ROXICODONE, and any opioid products upon which ROXICODONE's approval relied.**

There is no evidence that FDA considered the prior findings of safety and effectiveness for ROXYBOND's reference product, ROXICODONE, or for any other opioid product when determining whether to approve ROXYBOND. Indeed, in its opposition to PMRS's motion to complete and supplement the administrative record, FDA conceded that it did not consider whether any previously approved product upon which ROXYBOND's approval relies is safe and effective for use in the treatment of chronic pain.

C. There Is No Evidence that Prescription Opioids, As a Drug Class, Are Effective for the Treatment of Chronic Pain.

FDA defines chronic pain as "either pain persisting for longer than 1 month beyond resolution of the underlying insult, or pain persisting beyond 3 months [*i.e.*, 12 weeks]." *See* FDA00448-482. After conducting a comprehensive review of the scientific evidence supporting the purported effectiveness of long-term opioid therapy for chronic pain in 2016, the Centers for Disease Control and Prevention ("CDC") found 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.**

See Exhibit F at 1. Following its review, in its comprehensive March 2016 *Guideline for Prescribing Opioids for Chronic Pain*, the CDC concluded that "[t]he 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." FDA00573. The

CDC reported that "[t]he clinical evidence review found **insufficient evidence to determine long-term benefits of opioid therapy for chronic pain and found an increased risk for serious harms related to long-term opioid therapy that appears to be dose-dependent**." FDA00558 (emphasis added). As such, the CDC concluded 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." Exhibit F at 3.

In response to the CDC's report, FDA has acknowledged that "[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[,]" in contrast to the "growing evidence of harms associated with such use, and of the benefits of other nonopioid treatment alternatives." Exhibit A. Indeed, as FDA previously conceded, FDA "**is not aware of adequate and well-controlled studies of opioid use longer than 12 weeks**." Exhibit G, at 10. FDA has conceded that the performance and liabilities of opioids beyond 12 weeks have not been demonstrated "in the type of evidentiary base that FDA usually has for approval for when [the Agency] grant[s] an indication." Exhibit H, at 7-8.

D. PMRS'S Pending Citizen Petitions

Pursuant to 21 C.F.R. §§ 10.20 and 10.30, PMRS made recommendations to remedy the critical issues with FDA's approach to opioids via Citizen Petitions dated February 19, 2016, and March 6, 2017.[1] In its March 2017 Citizen 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

[1]PMRS's Citizen Petitions are pending under docket numbers FDA-2016-P-0645 and FDA-2017-P-1359. FDA00408-417, FDA00708-729.

pain, PMRS requested that the labeling of immediate release ("IR") opioid products state that the product is indicated for "acute pain for a limited duration."

In PMRS's February 2016 Citizen Petition, PMRS addressed the failings in FDA's approach of pursing abuse deterrent labeling without first addressing the significant risk posed by opioids used for the treatment of chronic pain. Specifically, 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." PMRS's own research and development has revealed systemic flaws with FDA's review and approval of opioids that are undermining FDA's ability to protect the public health and welfare in the face of the opioid-addiction epidemic. In its interim responses, FDA conceded that PMRS has raised complex issues of public policy and welfare. Yet FDA continues to approve opioids with labeling for chronic use, despite the health implications inherent in such conduct.

E. FDA's Approval of ROXYBOND is In Violation of the FDCA

As discussed above, FDA has been approving opioids for the treatment of chronic pain even though there is a lack of substantial evidence supporting the efficacy of these products in a chronic use setting, despite its obligations under the FDCA. PMRS has offered recommendations to FDA to remedy the critical failures with its approval processes. But rather than waiting until after completing its review of PMRS's pending Citizen Petitions and instead of addressing the lack of substantial evidence for labeling for chronic use, FDA instead moved ahead with approving yet another problematic opioid during the pendency of a raging health epidemic caused by opioid abuse.

The approval of ROXYBOND was not supported by new clinical studies demonstrating that ROXYBOND is an effective medication for the treatment of chronic pain. Instead,

ROXYBOND was approved through the 505(b)(2) pathway by relying on FDA's prior findings of safety and effectiveness for the reference product ROXICODONE . *See* Exhibit I at 1 (page 2 of the document). ROXICODONE's approval also was not based on new clinical studies demonstrating that the product is an effective medication for the treatment of chronic pain. *See* Exhibit J at 5 (page 6 of the document). Instead, ROXICODONE's approval relied upon FDA's prior findings of general analgesic effectiveness for the previously approved drug product PERCODAN. *Id.* Thus, the appropriateness of the approval of ROXICODONE for the treatment of chronic pain—and of products that reference it such as ROXYBOND—depends on the clinical studies supporting the efficacy of PERCODAN.

In contrast to single-entity oxycodone products such as ROXYBOND and ROXICODONE that are offered in 5-, 15-, and 30- mg tablets, PERCODAN is a combination product consisting of oxycodone (~5 mg) and aspirin (325 mg). *See* Exhibit K, at 2. Although FDA previously found PERCODAN to be an effective analgesic for the treatment of "moderate to moderately severe pain," (*see* Exhibit L), its approval does not support the expanded chronic pain indication and higher dosing of oxycodone suggested in the ROXYBOND labeling.

First, the current labeling for ROXYBOND—as well as that of its reference product ROXICODONE—indicates that the product is intended for use in the treatment of chronic pain. For example, the labeling states that, "For control of chronic pain, administer ROXYBOND on a regularly scheduled basis, at the lowest dosage level to achieve adequate analgesia." *See* Exhibit M, at 1. In contrast, neither the original nor current labeling for PERCODAN explicitly states that the product is intended for the treatment of chronic pain. *See generally* Exhibit K. Further, the regulatory history of PERCODAN indicates that no suitably controlled studies were submitted to support the effectiveness of PERCODAN for the treatment of **chronic** pain during

the DESI review process. *See* National Academy of Science/National Research Council (NAS/NRC), Panel on Drugs for Relief of Pain, Drug Efficacy Study Implementation (DESI) Review (PERCODAN, NDA 7337), at 2. Rather, PERCODAN's efficacy as a general analgesic for the treatment of "moderate to moderately severe" pain was apparently, in large part, assumed based on the general analgesic properties of oxycodone. For example, when evaluating the claim that PERCODAN is effective in the treatment of pain associated with "early cancer," the DESI Panel stated that, "Although the Panel is unfamiliar with any specific study to prove this point, it is not unreasonable to expect the claim to be true. The same might be said for almost any orally effective analgesic." *Id.*

Indeed, at the time of PERCODAN's approval in 1950, medical teaching advised that prescription opioids "should be avoided when treating chronic pain." Exhibit N, at 417. The medical community's concern about the long-term use of opioids to treat chronic pain was based on two factors: (1) "fear that chronic use would be associated with an unacceptably high risk of addiction" and (2) "a belief that neuropathic pain (which accounts for much chronic intractable pain) is not responsive to opioids." *Id.*

There are other significant issues with ROXYBOND's approval. The current labeling for ROXYBOND—as well as that of its reference product ROXICODONE—indicates that the total daily dose of oxycodone typically should be between 20-90 mg (based on the 5-mg and 15-mg tablets). *See* Exhibit M. However, ROXYBOND is also offered as a 30 mg tablet, which indicates a potential total daily dose of 120-180 mg of oxycodone. *Id.* In contrast, PERCODAN's labeling indicates that the total daily dose of oxycodone should usually be 20 mg. *See* Exhibit K, at 21. Importantly, the maximum daily dose of PERCODAN is considerably more limited in comparison to single-entity oxycodone products, such as ROXYBOND. The

labeling for PERCODAN states that a maximum of 12 tablets can be administered per day, which corresponds to a maximum daily dose of 60 mg of oxycodone. *Id.* Thus, neither the expanded chronic pain indication nor the high daily doses of oxycodone suggested in the ROXYBOND labeling are supported by FDA's prior findings of general analgesic efficacy for PERCODAN.

For these and other reasons, FDA should have required ROXYBOND's sponsor to submit new clinical studies to support the expanded chronic pain indication and the high daily doses suggested in the approved labeling. Given the lack of substantial evidence demonstrating the efficacy of ROXYBOND in the treatment of chronic pain, ROXYBOND's approval is in violation of the FDCA as a matter of law.

F. OXYCONTIN: An Example of a Flawed Process

On December 12, 1995, FDA approved OxyContin extended-release tablets (NDA 20-553) for treatment of "moderate to severe pain" where use of an "analgesic is appropriate for more than few days." *See Physician's Desk Reference* (53rd Ed., 1999, p 2572) Label for OxyContin, *Drug Abuse and Dependence (Addiction)*. FDA justified its approval of OxyContin 10mg, 20mg, and 40mg extended-release tablets based on a "delayed absorption" which it believed would "reduce the abuse liability of a drug." *Id.*; *see also* Exhibit R, April 11, 2018 PMRS Response to FDA Notice at 13. FDA used a single clinical trial comparing 10mg, 20mg, and placebo tablets as the substantial evidence of efficacy to reach this determination. *See id.* at 12. Section 14 of OxyContin's labeling states that studies were performed using a "double-blind, placebo-controlled, fixed-dose, parallel group, two-week study" to determine the effectiveness of this drug for treatment of chronic pain. (*See id.*). In that study, 10mg and 20mg tablets were used on patients to treat pain. 40 mg tablets were never tested. Patients reported that 20 mg, but not 10 mg tablets, were more effective in pain reduction. FDA approved not only

OXYCONTIN's 20 mg tablets, but also 10 mg tablets. FDA also approved OXYCONTIN's 40mg tablets that were never tested. *See id.* at 12-13.

More than twenty three (23) years have passed since OXYCONTIN extended-release tablets were initially released on the market, and there is still insufficient evidence to support the use of opioids for treatment of chronic pain. Despite the continued lack of scientific evidence to support the use of opioid products for treatment of chronic pain, on July 18, 2001, FDA changed the labeling for OxyContin and other opioids. Specifically, FDA supported labeling updates that changed the indication of OxyContin for treatment of acute pain to chronic pain. In support of their determination, FDA merely stated that the basis for this change was "to reinforce the appropriate patient population for whom this product is intended." *See* FDA00443. The appropriate patient population was defined by FDA as "patients suffering with chronic pain." FDA00419. Significantly, the label change still required the addition of a Box Warning to address the "concern over growing abuse, misuse and diversion of OxyContin tablets." *Id.* at 1. As this time, FDA also removed the "abuse-deterrent" language granted in the original label of this product. Notwithstanding, FDA maintained the labeling claims condoning the use of OXYCONTIN for treatment of chronic pain, without the support of new clinical data to back this up. FDA admitted that it was approving labeling on "belief" rather than substantial evidence of efficacy, which directly violates the Act's requirements. *See* 21 U.S.C. § 355(b); *see* Exhibit R.

G. Abuse-Deterrent Labeling Compounding the Problem

As discussed above, opioids are being approved with labeling for chronic use despite a lack of substantial evidence of efficacy for such use. Instead of addressing that critical problem, FDA has instead focused on applying multiple and inconsistent standards for evaluating abuse-deterrent properties of opioid products resulting in opposite decisions.

For example, in 2011, FDA rejected Opana ER (NDA 21-610) abuse-deterrent labeling for intranasal and intravenous abuse. Yet, that same year, FDA approved OxyContin NDA supplement (NDA 22-272/S-014) for abuse-deterrent labeling for crushing, breaking, intranasal, and intravenous abuse, expressly ignoring the fact that the reformulated Opana ER and OxyContin have virtually identical abuse-deterrent properties. Exhibit R at 7. FDA's rejection of Opana ER's abuse-deterrent labeling was at odds with its own findings. Specifically, FDA CSS evaluated reformulated Opana ER's abuse-deterrent properties by the intranasal route, which FDA relied on to reject the product's abuse-deterrent labeling. Remarkably, however, FDA simultaneously concluded that these studies showed reformulated Opana ER "support[s] a deterrent effect to abuse by the intranasal administration." *See id.* at 8.

In sharp contrast, and as explained by the studies outlined in PMRS's February 2016 Petition, OXYCONTIN does not have abuse-deterrent intranasal properties, but was approved for "abuse-deterrent" labeling by FDA. *See id.* FDA made the same inapposite determinations with respect to Opana ER and reformulated OxyContin's intravenous abuse-deterrent labeling, despite the virtually identical physiochemical properties between the two products. *See id.* This is a clear example of the FDA's application of inconsistent standards for evaluating abuse-deterrent properties, which is completely arbitrary and capricious.

In 2013, FDA amended the OXYCONTIN labeling once more, to incorporate a revised "abuse-deterrent" claim despite having withdrawn this claim in 2001. *See* FDA00665-697. FDA justified this determination by claiming that the controlled-released properties could be overcome with chewing and swallowing. In 2014, FDA required another labeling change to all ER opioids, including OXYCONTIN, whereby the indication was updated for use of "severe

pain enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate." *See* FDA00606-608.

More recently, in March 2016, the CDC conducted a comprehensive review of the scientific evidence supporting the effectiveness of long-term opioid therapy for chronic pain, and concluded that "[t]he few randomized trials to evaluate opioid efficacy for longer than 6 weeks had consistently poor results." Exhibit F. The CDC further reported that it found "insufficient evidence to determine long-term benefits of opioid therapy for chronic pain and found an increased risk for serious harms related to long-term opioid therapy that appears to be dose-dependent." *See* FDA00538-589.

High-ranking officials at FDA have made inconsistent statements about FDA's basis for evaluating and determining the abuse-deterrent intravenous properties of opioid products such as OXYCONTIN. For example, FDA's Division Director, Dr. Rappaport and FDA's Deputy Director, Dr. Throckmorten, made statements regarding FDA CSS's scientific findings about the abuse-deterrent properties of OxyContin. Specifically, CSS reported its evaluation of OxyContin's intravenous abuse-deterrent properties stating that "water is also effective in extracting oxycodone HC1 from intact tablets of reformulated OxyContin. Thus, a simple water extraction procedure can afford clinically significant amounts of oxycodone from high strengths of intact and crushed tablets of both the original and reformulated product." *See* Exhibit R at 8. Despite these findings, Dr. Rappaport stated, in support of abuse-deterrent labeling for this drug, that "these features also render the product almost impossible to dissolve, syringe and inject." *See id.* Similarly, Dr. Throckmorten concluded that "the in vitro testing was sufficient to demonstrate that OCR prevents oxycodone from being drawn into a syringe to any meaningful extent." (*See id.*). Not only are the conclusions of these high-ranking FDA officials at odds with

scientific evidence, they completely contradict FDA's own studies. FDA determined for itself that OxyContin could be readily prepared for injection, despite FDA's claims. *See id.* at 9-10.

H. FDA's Arbitrary and Capricious Denial of PMRS's PSA

PMRS filed its Petition for Stay of Action ("PSA) on May 11, 2017, seeking to stay the effective approval date approval date of ROXYBOND to consider the issues set forth in PMRS's pending Citizen Petitions and the stand-alone issues set forth in PMRS's PSA. In its denial of PMRS's PSA, FDA makes a sweeping and conclusory declaration that it does not need to consider the issues with its approval of opioids, as set forth above, until after completing its review of PMRS's pending Citizen Petitions and the substantive issues set forth in PMRS's PSA. In other words, FDA's position is to stay the course, figuring it out and fixing it later.

In denying PMRS's PSA, FDA refused to consider that opioid approvals for chronic use are in violation of the FDA. FDA argues that it should not have to consider whether there has been a fundamental violation of the FDCA until after it evaluates PMRS's recommendations to address such violations. Despite recognizing the critical public health issues implicit in PMRS's PSA and pending Citizen Petitions, FDA contends that it can continue to approve opioids without addressing the issues of approving opioids with labeling for chronic use and without addressing the serious issues of its approach to abuse deterrent labeling.

The "fire, aim, ready" approach that FDA is taking to these approvals will have a devastating impact on public health. FDA should have considered whether its actions with respect to opioids are in accordance with the FDCA. Instead, as FDA made clear in its opposition to PMRS's motion to complete the record and compel, it is taking the position that it does not have to determine whether it is in compliance with its statutory and regulatory obligations until after it evaluates PMRS's recommendations for remedying FDA's failure to comply with its statutory and regulatory obligations. FDA's approval of ROXICODONE—and,

thus, ROXYBOND—failed to satisfy the statutorily required level of evidence under the FDCA. *See* 21 U.S.C. 355(d) ("the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling"). FDA's refusal to consider that threshold fact in evaluating PMRS's PSA was arbitrary and capricious.

Rather than addressing that threshold issue, FDA instead offers only a conclusory and unsupported assertion that PMRS failed to establish sound public policy grounds supporting a stay, despite recognizing the fundamental public policy and health issues raised in PMRS's Citizen Petitions and PSA. Specifically, in its denial letter, FDA offered no explanation for its repeated approval of opioid drug products for the treatment of chronic pain, despite lacking substantial evidence to support the efficacy of these products in the chronic use setting. FDA also offered no explanation for its failure to adhere to its own existing recommendations for laboratory-based *in vitro* manipulation and extraction studies when evaluating opioid drug products with potentially abuse-deterrent properties. FDA offered no response to PMRS's arguments concerning FDA's troubling reliance on HAP studies, which are inherently flawed. FDA offered no response to PMRS's position regarding the dangers inherent in failing to require postmarketing proof of abuse-deterrent labeling before permitting labeling for abuse-deterrence.

FDA's failure to consider the threshold issue of compliance with the requirement that there be substantial evidence of efficacy before approving opioids with labeling for chronic use and abuse deterrence is fatally flawed. As such, FDA's decision must be reversed and ROXYBOND's effective approval date must be stayed.

III. PMRS'S PSA SATISFIES THE THRESHOLD REQUIREMENTS SET FORTH IN 21 CFR 10.35(E).

As discussed above, FDA's failure to consider threshold statutory issues in evaluating PMRS's PSA was arbitrary and capricious. The PSA satisfied the requirements in FDA's governing regulations. As such, PMRS's PSA should have been granted as a matter of law.

Pursuant to 21 CFR 10.35(e), a stay should be granted if the following four factors are shown: (1) "The petitioner has demonstrated sound public policy grounds supporting the stay"; (2) "The delay resulting from the stay is not outweighed by public health or other public interests"; (3) "The petitioner's case is not frivolous and is being pursued in good faith"; and (4) "The petitioner will otherwise suffer irreparable injury." 21 CFR 10.35(e)(1)-(4). Here, PMRS has properly demonstrated the existence of each of these elements, and FDA's decision to deny PMRS' PSA was therefore arbitrary and capricious as a matter of law.

A. PMRS Sufficiently Demonstrated Sound Public Policy Grounds to Support the Stay.

PMRS adequately demonstrated public policy grounds that supported granting its PSA and FDA erred in denying that Petition. Granting PMRS' PSA would serve to further protect the public health interest by ensuring that additional opioid drug products are not permanently added to the market before their efficacy and safety is adequately established in a scientifically rigorous manner. There is also a strong public policy 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 for these products. Statements from medical professionals at advisory committee meetings have expressed that view. 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." *See* FDA00259-368.

Moreover, as detailed in PMRS' Citizen Petitions and PSA, 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." *See* Exhibit A at 1. Even the daily news is replete with articles about the abuse of opioids and the skyrocketing toll it is taking on public health. In light of this reality, the issues raised in PMRS' submissions must be addressed before ROXYBOND is launched to help cure this serious crisis.

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.

Critically, FDA acknowledged in its denial letter that "opioid addiction and the resulting overdoses and deaths have created a national crisis", (FDA00378), and that "Commissioner Gottlieb has recently said that reducing the scope of the epidemic of opioid addiction is his highest immediate priority as Commissioner", (*id.*). Despite acknowledging this epidemic, FDA stated that it did not believe that granting a stay to critically analyze its review process of opioids and the ROXYBOND application to ensure its safety "would be an appropriate response to this crisis." FDA00379. Instead, FDA explained that it was taking other measures to improve the

problem. However, none of the actions it explained actually involve reviewing or improving the standards by which it reviews opioids for certain labeling indications. Indeed, FDA explained that it was "working to enhance prescriber and patient awareness of the safe use of opioids," and "undertaking a study to improve its understanding of prescriber beliefs relating to use of opioid products with abuse-deterrent properties." FDA00378-379. Increasing user awareness and its own understanding of prescriber beliefs does not address or correct the foundational problem at issue, that FDA is improperly approving opioids for abuse-deterrent and chronic use labelling in the first place.

Because PMRS properly demonstrated sound public policy grounds to support its PSA, and the FDA relied on inapposite considerations to ignore those facts, the Court should find that FDA acted arbitrarily and capriciously as a matter of law when it refused to stay the approval of ROXYBOND.

B. Any Delay That Would Result From a Stay is not Outweighed by Public Health or Other Interests.

PMRS merely sought a temporary stay of the approval, and subsequent dissemination into the marketplace, of ROXYBOND until the legitimate concerns that were raised in its Citizen Petitions and PSA were properly reviewed and resolved by the FDA. Any delay that may result from granting the stay is minimal and inconsequential compared to the great public interest that would be served. Interestingly, the FDA completely failed to address this element in its denial letter. While FDA "believe[s] that the approval of ROXYBOND is a step forward in the Agency's broader efforts to combat opioid abuse and misuse," (FDA00379), it fails to appreciate the dangers attendant to the dissemination of an IR opioid that has not been rigorously reviewed under the appropriate stringent standards.

Practically speaking, ensuring that ROXYBOND's labeling indications are supported by sufficient data prior to dissemination furthers FDA's "highest immediate priority" "to address this public health concern" and reduce "the scope of the epidemic of opioid addiction." FDA00378. FDA fails to provide any reason for this Court to hold otherwise. Furthermore, Inspirion and Daiichi serve to benefit from a temporary stay, as assurance from FDA that ROXYBOND's labeling is accurate will help shield these companies from future liability on that issue. As explained at great length in PMRS' PSA and below, there is not sufficient information at the moment to affirmatively support ROXYBOND's claims relating to chronic use and abuse-deterrence. Halting the launch of this product, then, would help prevent future lawsuits relating to these deceiving misrepresentations. Moreover, the public policy considerations, explained above, are too great to be ignored.

Balancing the minor delay that would result with the greater public health that will be advanced, PMRS demonstrated as a matter of law that a stay should be granted.

C. PMRS' Case is Not Frivolous and Is Being Pursued in Good Faith.

There is no question, and FDA does not deny, that PMRS pursued its PSA in good faith. The Petition was predicated, in part, upon PMRS' then-pending Citizen Petitions, which were grounded in substantive scientific and legal arguments, and which addressed valid issues with FDA's review and approval process of opioids. FDA has acknowledged this fact. In its interim response to PMRS' February 2016 Petition, FDA stated that it "has been unable to reach a decision on [PMRS'] petition because it raises complex issues requiring extensive review and analysis by Agency officials." *See* FDA00991. Beyond the legitimate scientific and legal arguments that were raised in the Citizen Petitions, PMRS' PSA raises additional concerns that are specific to ROXYBOND and are based on sound theories which legitimately challenge the validity of that drug's approval with labeling indications for the treatment of chronic pain and

abuse-deterrence properties. For these reasons, PMRS' case is not frivolous and is being pursued in good faith.

D. PMRS Established That it Will Suffer Irreparable Injury and FDA's Finding to the Contrary has No Basis in Law or Fact.

The launch of ROXYBOND prior to FDA's appropriate consideration and resolution of the issues raised in PMRS' PSA will cause irreparable injury to PMRS and the public at large. In denying PMRS' arguments on this point, it "entirely failed to consider [] important aspect[s] of the problem, [and] offered an explanation for its decision that runs counter to the evidence before" it. *Motor Vehicle Mfrs. Ass'n of U.S., Inc.*, 463 U.S. at 43. As such, the Court should find as a matter of law that FDA acted arbitrarily and capriciously.

First, the uninterrupted approval of ROXYBOND will fundamentally alter the landscape for opioid drugs and have an immediate negative impact on PMRS' business reputation, sales and goodwill. Indeed, it is well-established that "[g]rounds for irreparable injury include loss of control of reputation, loss of trade, and loss of goodwill." *Pappan Enters, Inc. v. Hardee's Food Sys.*, 143 F.3d 800, 805 (3d Cir. 1998); *Opticians Ass'n v. Indep. Opticians*, 920 F.2d 187, 195 (3d Cir. 1990) (same). Here, 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 on the marketplace in relation to other appropriately studied and labeled IR products formulated with "abuse-deterrent" properties. *See, e.g.*, *Hill Dermaceuticals, Inc.*, 524 F. Supp. 2d 5, 12 (D.C.

2007). This is a detrimental consequence that PMRS will have absolutely no control over, and serves as irrefutable evidence of irreparable injury.

Second, the launch of ROXYBOND will have an immediate and significant impact on the market and on PMRS' investment in research and development, particularly in light of the current public disclosure 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, the risk of which is to cause confusion and injure the public health. Most critically, PMRS will not be able to recoup these losses from FDA or any other individual or entity in the form of monetary damages as these injuries are difficult, if not impossible, to calculate. S*ee FMC Corp. v. Control Solutions, Inc.*, 369 F. Supp. 2d 539, 573 (E.D.Pa. 2005) ("Competitive injuries and loss of goodwill are types of injuries that are difficult to quantify"). The inability to quantify that adverse impact and the lack of an avenue by which to recoup such losses is an irreparable injury that PMRS will surely endure.

Third, FDA's refusal to stay the launch of ROXYBOND 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. *See e.g.*, *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."). For example, 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 the range of abuse-deterrent and non-abuse-deterrent products on the market at the time of that application." FDA00736 (emphasis added). Furthermore, PMRS faces a real risk that its product will be inappropriately compared to other abuse-deterrent products – such as ROXYBOND – whose approvals were based on limited evidence of efficacy or meaningful abuse-deterrent properties. FDA states in 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." FDA00756 (emphasis added).

As these facts demonstrate, PMRS will be irreparably harmed due to FDA's denial of PMRS' PSA. Yet, in three conclusory paragraphs, FDA disagreed. FDA00372-379. Indeed, without specifically addressing or explaining the issues that PMRS raised, FDA stated that "[n]one of the allegations or information in the PSA demonstrate that PMRS will suffer irreparable injury absent a stay of ROXYBOND's approval." *Id.* To support its finding, FDA blankly claimed that it disagreed with the contention that ROXYBOND is a "less safe and effective drug" and that its approval for abuse-deterrent labeling was not properly supported. *Id.* This contention, however, does not address the concerns related to the loss of goodwill, market share opportunities, and investment already spent in research and development. Nor does it tackle the undeniable challenges that PMRS will face during the approval process of its product that it would not normally be required to overcome because of the improper prior approval of ROXYBOND. Instead, FDA merely refers PMRS to the agency's review documents for ROXYBOND *in a footnote* and concludes with the notion that it is not certain whether PMRS' own drug application will be approved and if so, when. *Id.* This brief, vague response, and

subsequent decision, cannot plausibly be considered anything but arbitrary and capricious under the law.

Because PMRS adequately demonstrated that it will suffer irreparable injury if its Petition is not granted, and FDA inadequately acknowledged and addressed that fact, the Court should find that the Agency's ultimate decision to deny the PSA was arbitrary and capricious as a matter of law.

CONCLUSION

For the reasons set forth herein, PMRS respectfully requests that this Court enter summary judgment in its favor.

Dated: July 2, 2018

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IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF PENNSYLVANIA

PHARMACEUTICAL MANUFACTURING RESEARCH SERVICES, INC., Plaintiff-Petitioner, v. UNITED STATES FOOD AND DRUG ADMINISTRATION, SCOTT GOTTLIEB, M.D., in his official capacity as the Commissioner of Food and Drugs, and his successors and assigns, and ERIC D. HARGAN, in his official capacity as the Acting Secretary of the United States Department of Health and Human Services, as well as his successors and assigns, Defendants.	**Civil Action No. 2:17-cv-4898-GJP** **PLAINTIFF PHARMACEUTICAL MANUFACTURING RESEARCH SERVICES, INC.'S RULE 56.1 STATEMENT OF UNDISPUTED MATERIAL FACTS**

Pursuant to Local Civil Rule 56.1, Plaintiff Pharmaceutical Manufacturing Research Services, Inc. (hereinafter "PMRS"), hereby makes the following Rule 56.1 Statement of Undisputed Material Facts with citations to supporting materials.

1. Plaintiff-Petitioner PMRS is a corporation with headquarters located at 202 Precision Road, Horsham, Pennsylvania 19044.

2. As a world-class supplier of pharmaceutical services, PMRS supports the manufacturing of four FDA-approved drug products, two internationally-approved drug products, and numerous developmental and investigational drugs.

3. PMRS is a DEA-registered manufacturer of schedule 2 products.

4. PMRS has held such licensing for more than 22 years, manufacturing controlled substances for a variety of pharmaceutical companies.

5. PMRS actively has been involved in the research, development, and commercial manufacturing of opioids for abuse-deterrence for more than a decade.

6. PMRS has been issued two (2) patents from the United States Patent and Trademark Office for opioids formulated for abuse-deterrence and has another four (4) such patents pending.

7. Defendant FDA is an agency responsible for, among other duties, protecting the public health by ensuring the safety, efficacy, and security of human and veterinary drugs, biological products, and medical devices.

8. FDA's headquarters are located at 10903 New Hampshire Avenue, Silver Spring, Maryland 20993.

9. FDA is headed by Defendant Scott Gottlieb, M.D., Commissioner of Food and Drugs, and operates under authority delegated by Congress and Defendant Eric D. Hargan, in his official capacity as the Acting Secretary of the United States Department of Health and Human Services ("HHS"), a federal agency headquartered in the District of Columbia.

10. Commissioner Gottlieb and Acting Secretary Eric Hargan, who since has been replaced by Secretary Azar, and their respective successors and assigns, are sued in their official capacities as the government officials with ultimate responsibility for the actions and failures to act complained of herein.

A. <u>The Opioid Epidemic and Its Impact on the Public Health</u>

11. The United States of America is mired in a catastrophic opioid epidemic.[1] *See* Exhibit A, Robert M. Califf, M.D., et al., *A Proactive Response to Prescription Opioid Abuse*, 374 N. Engl. J. Med. 1480, 1483-85 (2016).

[1] "Opioids" are prescription painkillers in the opiate class.

12. Statistics compiled by the Centers for Disease Control and Prevention ("CDC") demonstrate that, in 2014 alone, almost 2,000,000 Americans abused or were dependent on prescription opioids and that opioids killed more than 33,000 people in 2015, more than any previous year on record.

13. CDC also reports that the number of opioid-related overdose deaths has quadrupled since 1999 and that 91 Americans die every day from an opioid overdose.

14. The public health crisis caused by the opioid epidemic has led to substantial economic harm as well.

15. For example, the White House Council of Economic Advisers (CEA) recently reported that in 2015, the economic cost of the opioid crisis was $504.0 billion, or 2.8 percent of GDP that year. *See* Exhibit B, Council of Economic Advisers, *The Underestimated Cost of the Opioid Crisis* (November 2017), at 1, https://www.whitehouse.gov/the-press-office/2017/11/20/cea-report-underestimated-cost-opioid-crisis (last visited June 30, 2018).

16. That figure was over six times larger than the previous estimate of the economic cost of the epidemic. (*Id.*)

17. Analysis of opioid-related economic harms at the state level indicates that Pennsylvania ranks among the top 10 states in terms of total health care spending related to opioid abuse, with conservative estimates suggesting that the state spends $847 million per year on these costs—most likely significantly higher when the costs of opioid-abuse-related criminal justice and lost workplace productivity are taken into account. *See* Exhibit C, Matrix Global Advisors, *Health Care Costs from Opioid Abuse: A State-by-State Analysis*, at 2-4 (Apr. 2015), https://drugfree.org/wp-content/uploads/2015/04/Matrix_OpioidAbuse_040415.pdf (last visited June 30, 2018).

18. In 2016, drug-related overdose deaths in Pennsylvania increased by 37 percent from 2015, and the Pennsylvania drug-related overdose death rate remained significantly higher than the national average. *See* Exhibit D, DEA, *Analysis of Overdose Deaths in Pennsylvania, 2016* (Jul. 2017), at 5, https://www.overdosefreepa.pitt.edu/wp-content/uploads/2017/07/DEA-Analysis-of-Overdose-Deaths-in-Pennsylvania-2016.pd_-1.pdf (last visited June 30, 2018).

19. Philadelphia led the nation in 2015 in drug overdose deaths among young adult men. *See* Exhibit E, Don Sapatkin, *Pa. leads nation in young men's overdose deaths, N.J. 4th*, The Philadelphia Inquirer (updated Nov. 20, 2015, 1:08 AM EST), http://www.philly.com/philly/health/addiction/20151120_Pa___N_J__lead_nation_in_young_men_s_overdose_deaths.html (last visited June 30, 2018).

20. On October 26, 2017, in response to the escalating crisis, President Donald J. Trump directed the Department of Health and Human Services to declare the opioid crisis a public health emergency.

21. President Trump noted that, "[n]o part of our society – not young or old, rich or poor, urban or rural – has been spared this plague of drug addiction and this horrible, horrible situation that's taken place with opioids."

22. Accordingly, President Trump declared the opioid epidemic "a national health emergency."

23. FDA's entrenched regulatory approach is unlawful and has significantly contributed to this national health emergency.

B. Prescription Opioids, such as ROXYBOND, Have Not Been Demonstrated to be Effective Medications for the Treatment of Chronic Pain

24. FDA defines chronic pain as "either pain persisting for longer than 1 month beyond resolution of the underlying insult, or pain persisting beyond 3 months." *See* FDA00453.

25. Critically, however, after conducting a comprehensive review of the scientific evidence supporting the effectiveness of long-term opioid therapy for chronic pain, the CDC found 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.

Exhibit F, Thomas R. Frieden & Debra Houry, *Reducing the Risks of Relief — The CDC Opioid-Prescribing Guideline*, 374 New Eng. J. Med. 1501, 1501 (2016).

26. Indeed, in its comprehensive March 2016 *Guideline for Prescribing Opioids for Chronic Pain*, the CDC found that "[t]he 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." FDA00573, CDC, *Guideline for Prescribing Opioids for Chronic Pain*, at p. 34 of document (2016), https://www.cdc.gov/mmwr/volumes/65/rr/pdfs/rr6501e1.pdf (last visited June 30, 2018).

27. The CDC also reported that "[t]he clinical evidence review found insufficient evidence to determine long-term benefits of opioid therapy for chronic pain and found an increased risk for serious harms related to long-term opioid therapy that appears to be dose-dependent." FDA00558.

28. Thus, the CDC concluded 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." Exhibit F, Frieden & Houry, *Reducing the Risks of Relief — The CDC Opioid-Prescribing Guideline*, 374 New Eng. J. Med. at 1503.

29. In response to the CDC's report, FDA has acknowledged that "[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[,]" in contrast to the "growing evidence of harms associated with such use, and of the benefits of other nonopioid treatment alternatives." Exhibit A, Robert M. Califf et al., *A Proactive Response to Prescription Opioid Abuse*, 374 New Eng. J. Med. at 1484.

30. Indeed, as FDA has previously conceded, the Agency "is not aware of adequate and well-controlled studies of opioid use longer than 12 weeks." Exhibit G, FDA Response to Physicians for Responsible Opioid Prescribing (PROP) Citizen Petition (Sep. 10, 2013), at 10, https://www.regulations.gov/document?D=FDA-2012-P-0818-0793 (last visited June 30, 2018).

31. FDA has also conceded that the performance and liabilities of opioids beyond 12 weeks have not been demonstrated "in the type of evidentiary base that FDA usually has for approval for when [the Agency] grant[s] an indication." Exhibit H, FDA, Transcript, *Assessment of Analgesic Treatment of Chronic Pain: A Scientific Workshop* (May 31, 2012), at 7-8 (statement of Janet Woodcock, M.D., Director, CDER), https://www.regulations.gov/document?D=FDA-2012-N-0067-0017 (last visited June 30, 2018).

32. In sum, FDA has acknowledged that the Agency "does its best work when high-quality scientific evidence is available to assess the risks and benefits of intended uses of medical products" but that "[u]nfortunately, the field of chronic pain treatment is strikingly deficient in such evidence." Exhibit A, Robert M. Califf et al., *A Proactive Response to Prescription Opioid Abuse*, 374 New Eng. J. Med. at 1484.

33. In stark contradiction to both the CDC's findings and its own public statements, FDA continues to approve new opioid products intended for the treatment of chronic pain.

34. The approval of ROXYBOND was not supported by new clinical studies demonstrating that ROXYBOND is an effective medication for the treatment of chronic pain. *See* Exhibit I, *Medical Review (NDA 20977)*, at 1, https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/209777Orig1s000MedR.pdf (last visited June 30, 2018).

35. Instead, ROXYBOND's approval relied upon FDA's prior findings of analgesic effectiveness for the reference listed drug (RLD) ROXICODONE. (*Id.*)

36. ROXICODONE's approval, however, also is not based on new clinical studies demonstrating that the product is an effective medication for the treatment of chronic pain. *See* Exhibit J, *Medical Review (NDA 21-011/AZ), Response to AE Letter* (June 22, 2000), at 5, https://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/21-011_Roxicodone_Medr_P1.pdf (last visited June 30, 2018).

37. Instead, ROXICODONE's approval relied upon FDA's prior findings of general analgesic effectiveness for the approved RLD product PERCODAN. *Id.*

38. Thus, the legality of the approval of ROXICODONE for the treatment of chronic pain—and of products that reference it such as ROXYBOND—depends on the clinical studies supporting the efficacy of PERCODAN.

39. In contrast to single-entity oxycodone products such as ROXYBOND and ROXICODONE that are offered in 5-, 15-, and 30- mg tablets, PERCODAN is a combination product consisting of oxycodone (~5 mg) and aspirin (325 mg). *See* Exhibit K, PERCODAN 2016 Labeling, at 2, https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/007337s049lbl.pdf (last visited June 30, 2018).

40. FDA originally determined through the DESI review process that PERCODAN is an effective analgesic for the treatment of "moderate to moderately severe pain.". *See* Exhibit L, DESI Amended Classification Notice (PERCODAN, NDA 7337), 37 Fed. Reg. 26356, 26356 (Dec. 9, 1972).

41. While its current labeling states that the product is "indicated for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate," PERCODAN's labeling does not include the chronic use language present in ROXYBOND's labeling or suggest the higher dosages of oxycodone present in that labeling. *See* Exhibit K, PERCODAN 2016 Labeling, at 6 & 21, https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/007337s049lbl.pdf (last visited June 30, 2018).

42. The labeling for ROXYBOND—as well as that of its reference product ROXICODONE—explicitly indicates that the product is intended for use in the treatment of chronic pain. For example, the Highlights section of the labeling states that, "For control of chronic pain, administer ROXYBOND on a regularly scheduled basis, at the lowest dosage level to achieve adequate analgesia." *See* Exhibit M, ROXYBOND 2017 Labeling, at 1, https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209777lbl.pdf (last visited June 30, 2018).

43. Further, the Dosage and Administration section of ROXYBOND's labeling states that, "For control of severe chronic pain, consider dosing ROXYBOND on a regularly scheduled basis, every 4 to 6 hours, at the lowest dosage level that will achieve adequate analgesia." *Id.* at 4.

44. Moreover, the regulatory history of PERCODAN indicates that no suitably controlled studies were submitted as part of the DESI review to support the effectiveness of PERCODAN for the treatment of any pain indication—including the indication of chronic pain—with the exception of a study submitted for the indication of postpartum pain. National Academy of Science/National Research Council (NAS/NRC), Panel on Drugs for Relief of Pain, Drug Efficacy Study Implementation (DESI) Review (PERCODAN, NDA 7337), at 2.

45. Rather, PERCODAN's efficacy as a general analgesic for the treatment of "moderate to moderately severe" pain was apparently, in large part, assumed based on the general analgesic properties of oxycodone.

46. For example, when evaluating the claim that PERCODAN is effective in the treatment of pain associated with "early cancer," the DESI Panel stated that, "Although the Panel is unfamiliar with any specific study to prove this point, it is not unreasonable to expect the claim to be true. The same might be said for almost any orally effective analgesic." *Id.*

47. Moreover, at the time of PERCODAN's approval in 1950, medical teaching advised that prescription opioids "should be avoided when treating chronic pain." Exhibit N, Jane C. Ballantyne, "Safe and effective when used as directed": the case of chronic use of opioid analgesics, 8 J Med Toxicol. 417, 417 (2012), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3550253 (last visited June 30, 2018).

48. The medical community's concern about the long-term use of opioids to treat chronic pain was based on two factors: (1) "fear that chronic use would be associated with an unacceptably high risk of addiction" and (2) "a belief that neuropathic pain (which accounts for much chronic intractable pain) is not responsive to opioids." *Id.*

49. A key catalyst of the use of opioids to treat chronic pain was the approval of OXYCONTIN in December 1995. "When Purdue Pharma introduced OxyContin in 1996, it was aggressively marketed and highly promoted. Sales grew from $48 million in 1996 to almost $1.1 billion in 2000." Exhibit O, Art Van Zee, *The Promotion and Marketing of OxyContin: Commercial Triumph, Public Health Tragedy*, 99 Am J Public Health 221, 221 (2009), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2622774/ (last visited June 30, 2018).

50. The current labeling for ROXYBOND—as well as that of its reference product ROXICODONE—indicates that the total daily dose of oxycodone typically should be between 20-90 mg (based on the 5-mg and 15-mg tablets). *See* Exhibit M, ROXYBOND 2017 Labeling, at 1, https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209777lbl.pdf (last visited June 30, 2018).

51. However, ROXYBOND is also offered as a 30 mg tablet, which indicates a potential total daily dose of 120-180 mg of oxycodone. *Id.*

52. In contrast, PERCODAN's labeling indicates that the total daily dose of oxycodone should usually be 20 mg. *See* Exhibit K, PERCODAN 2016 Labeling, at 21, https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/007337s049lbl.pdf (last visited June 30, 2018).

53. Further, the maximum daily dose of PERCODAN is considerably more limited in comparison to single-entity oxycodone products, such as ROXYBOND. The labeling for PERCODAN states that a maximum of 12 tablets can be administered per day, which corresponds to a maximum daily dose of 60 mg of oxycodone. *Id.*

54. For these reasons, neither the expanded chronic pain indication nor the high daily doses of oxycodone suggested in the ROXYBOND labeling are supported by FDA's prior findings of general analgesic efficacy for PERCODAN.

55. Because PERCODAN is not an appropriate reference product for ROXICODONE—and, by extension, ROXYBOND-- FDA should have required ROXYBOND's sponsor to submit new clinical studies to support the expanded chronic pain indication and the high daily doses suggested in the approved labeling.

56. Given the lack of substantial evidence demonstrating the efficacy of ROXYBOND in the treatment of chronic pain, ROXYBOND's approval is in violation of the FDCA.

57. In turn, FDA's refusal to stay the effective approval date of ROXYBOND to consider the issues set forth in PMRS's pending Citizen Petitions and the stand-alone issues set forth in PMRS's PSA is particularly troubling.

58. FDA's approval of ROXYBOND is also in violation of the FDCA because, as a combination product, PERCODAN is not an appropriate reference product for single-entity oxycodone IR products such as ROXICODONE and ROXYBOND.

59. During its review of the original application submitted for ROXICODONE—the reference product for ROXYBOND—FDA found the application deficient because "[n]o data to support effectiveness were included in the [application] as [the] comparative studies included only . . . **unapproved** 5 mg [oxycodone] tablets." Exhibit P, Center for Drug Evaluation and Research, Application Number 21-011, Administrative Documents, Memorandum from B. Rappaport, M.D. to File, *Supervisory Review of NDA 21-011, Response to Approvable Letter, for ROXICODONE (oxycodone HCL) 15 and 30 mg tablets* (Aug. 31, 2000), at 1 (page 25 of the

document), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/21-011_Roxicodone_Admindocs_P1.pdf (last visited June 30, 2018) (emphasis added).

60. FDA concluded that the 5-mg oxycodone tablets used in the comparative studies submitted in the original ROXICODONE application could not be relied upon to demonstrate efficacy because, while marketed, the product had never been approved and was "neither a grandfathered nor a DESI drug." Exhibit P, Center for Drug Evaluation and Research, Application Number 21-011, Administrative Documents, Memorandum from C. McCormick, M.D. to File, *Roxicodone™ IR (Oxycodone Hydrochloride Tablets USP Immediate Release 15 mg, and 30 mg)* (Sep. 16, 1999), at 5 (page 35 of the document), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/21-011_Roxicodone_Admindocs_P1.pdf (last visited June 30, 2018).

61. Although ROXICODONE was ultimately approved based on the prior efficacy findings of the approved product PERCODAN, FDA commented during its review of the original ROXICODONE application that referencing "a more recent [product] with specific data demonstrating the **separate** contribution of oxycodone 5-mg to efficacy would be preferable." *Id.* at 4 (page 34 of the document) (emphasis added).

62. As FDA explained, "oxycodone exists in the marketplace in many forms by virtue of DESI evaluation of the immediate release product, 5mg, **in combination with aspirin (Percodan).**" *Id.* at 1 (page 31 of the document) (emphasis added).

63. However, the "currently available oxycodone [immediate-release] 5-mg product that is being marketed as a **single entity** analgesic has no historical basis for approval." *Id.* (emphasis added).

64. Indeed, FDA commented that the "dilemma" presented by the original ROXICODONE application was "the paucity of findings of efficacy of oxycodone **apart from an analgesic mixture [i.e., PERCODAN]**, and the studies linking this product to an **unapproved drug [i.e., 5-mg single-entity IR oxycodone]**." *Id.* at 4 (page 34 of the document) (emphasis added).

65. The "preferable alternative" to establishing efficacy by relying on PERCODAN was, according to FDA, for ROXICODONE's sponsor to "provide clinical trials for any of the [single-entity oxycodone] IR dosage forms (5 mg, 15 mg and 30 mg)." *Id.* at 5 (page 35 of the document).

66. FDA should not have permitted a single-entity oxycodone IR product such as ROXICODONE—and, by extension, ROXYBOND—to rely upon a combination product, such as PERCODAN, because the specific contribution of oxycodone to the overall efficacy of the combination of the two active ingredients in PERCODAN was never determined.

67. Accordingly, FDA's approval of ROXICODONE—and, thus, ROXYBOND—failed to satisfy the statutorily required level of evidence under the FDCA. *See* 21 U.S.C. 355(d) ("the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling").

C. PMRS's Citizen Petitions

68. PMRS's own research and development activities have revealed fundamental flaws with FDA's review and approval of opioids that are undermining FDA's ability to protect the public health and welfare in the face of the opioid-addiction epidemic.

69. Pursuant to 21 C.F.R. §§ 10.20 and 10.30, PMRS raised those critical issues with FDA via Citizen Petitions dated February 19, 2016, and March 6, 2017.[2]

70. In its interim response, FDA itself acknowledged that issues raised by PMRS in its Citizen Petitions are complex.

71. Yet in its denial of PMRS's PSA, FDA makes a sweeping and conclusory declaration that neither Citizen Petition warrants staying the effective approval date of ROXYBOND.

72. In other words, FDA's position is to stay the course, figuring it out and fixing it later.

73. On February 19, 2016, PMRS submitted a citizen petition to FDA directed at the issue of abuse-deterrent labeling ("February 2016 Citizen Petition"), pending under Docket No. FDA-2016-P-0645, requesting, in part, that FDA take certain actions, summarized as follows:

a. 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;

b. Remove Category 3 human abuse-deterrent (liking) studies from the FDA Guidance, "Abuse-Deterrent Opioids Evaluation and Labeling Guidance for Industry" (April 2015), and as a requirement for approval of drug products with potentially abuse deterrent properties as inherently flawed, subjective, and highly prone to manipulation; and

c. 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.

[2] PMRS's Citizen Petitions are pending under docket numbers FDA-2016-P-0645 and FDA-2017-P-1359. *See* FDA00408-417, FDA00708-729.

74. PMRS's February 2016 Citizen Petition 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.[3]

75. On March 6, 2017, PMRS submitted a citizen petition to FDA directed at the issue of chronic-use labeling, now pending under Docket No. FDA-2017-P-1359 ("March 2017 Citizen Petition"), requesting, in part, the revocation of all immediate-release ("IR") opioid drug product labeling that "support[s] use for the treatment of chronic pain." PMRS further requested that all IR opioid drug product labeling state that the indication is for "acute pain for a limited duration."

76. PMRS has raised the above-discussed issues directly with FDA on multiple occasions, publicly advocating for the agency to reassess its approach to approving opioid products.

77. In addition to its two Citizen Petitions, PMRS also has participated in numerous FDA Advisory Committee meetings and public workshops. *See generally* PMRS's comments at the advisory committee meetings pertaining to VANTRELA ER (June 7, 2016), TROXYCA ER (June 8, 2016), ARYMO ER (Aug. 4, 2016), the use of opioids in pediatric patients (Sep. 16, 2016), OPANA ER (Mar. 14, 2017), ROXYBOND (Apr. 5, 2017), and REXISTA (Jul. 26, 2017), as well as the public meeting on premarket evaluation of abuse-deterrent properties (Nov. 1, 2016).

[3] In addition, the February 2016 Petition included a request for actions pertaining to OXYCONTIN specifically. (February 2016 Petition, No. FDA-2016-P-0645 at 4.) The OXYCONTIN-specific requests are not addressed in this action.

78. To date, however, PMRS has received no substantive response to its Citizen Petitions and, thus, no explanation for FDA's continuation of a seemingly status quo approach that permits flooding the market with opioids labeled as abuse-deterrent and appropriate for chronic use, despite the absence of sufficient data to support those claims.

D. PMRS's May 11, 2017 Petition for Stay of Action

79. Notwithstanding the significant public-health issues discussed in PMRS's various submissions, and notwithstanding FDA's acknowledgment of CDC's findings confirming the lack of sufficient data to support use of opioids to treat chronic pain, on April 20, 2017, FDA approved Inspirion's NDA for ROXYBOND.

80. On May 11, 2017, PMRS submitted a Petition for Stay of Action ("PSA") to FDA. *See* FDA00001-31, May 11, 2017 PSA.

81. The PSA sought a stay of the effective approval date of ROXYBOND tablets with labeling claims pertaining to chronic use and abuse deterrence until FDA issued substantive responses to: (1) issues raised in its PSA related to the ROXYBOND approval, and (2) the two pending Citizen Petitions submitted by PMRS. FDA00001.

82. PMRS argued that approving ROXYBOND was directly contrary to the issues raised in its Citizen Petitions. FDA00002-3.

83. First, PMRS argued that FDA should stay the approval of ROXYBOND because it was not in accordance with FDA's laws and regulations as it was approved with chronic use labeling. *See, e.g.*, FDA00004 ("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").

84. Second, PMRS argued that FDA should stay the approval of ROXYBOND because it was not in accordance with FDA's laws and regulations as it was approved with labeling supporting abuse-deterrent claims. *See, e.g.*, FDA00004 ("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").

85. Third, PMRS argued that FDA should stay the approval of ROXYBOND because, even assuming *arguendo* that FDA's approach to approving opioids was lawful, ROXYBOND's approval failed to comply with FDA's own Guidance documents for evaluating purported abuse-deterrent opioid formulations. *See, e.g.*, FDA00004 ("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.**") (emphasis added).

86. In addition to its arguments regarding chronic use and abuse-deterrent labeling, PMRS provided numerous additional grounds for why ROXYBOND's approval did not comply with FDA's existing laws, regulations, and Guidance documents.

87. First, PMRS argued that the design of ROXYBOND's particle size manipulation study was arbitrary because, contrary to FDA's recommendations, it used a target particle size criteria of less than 2000 microns, instead of less than 500 microns. FDA00007-12.

88. PRMS also argued that the arbitrary design of the particle size manipulation study resulted in the wrong tool being used to prepare manipulated product for use in the subsequent in vitro studies and clinical studies. *Id.*

89. Second, PMRS argued that the ROXYBOND extraction study was incomplete because, contrary to FDA's recommendations, the study failed to fully investigate other non-sophisticated manipulations by which opioid might be extracted from intact ROXYBOND tablets and then recovered in solid form from this solution and which would allow a non-sophisticated abuser to extract and inject the product. FDA00012-13.

90. Third, PMRS argued that the ROXYBOND syringeability study was incomplete because the study did not fully investigate whether other known methods for extracting opioid from intact ROXYBOND tablets could be used by non-sophisticated abusers to prepare solutions suitable for injection by intravenous or subcutaneous routes. FDA00013-15.

91. Fourth, PMRS argued that the HAP study relied upon by FDA to approve ROXYBOND was inherently flawed because of the substantial difference in the volume of the tablets used in the study which precluded the proper blinding of test subjects. FDA00015-16.

92. Fifth, PMRS argued that FDA should have required ROXYBOND to provide post-marketing evidence of abuse-deterrent properties before approving abuse-deterrent labeling. FDA00016-18.

93. Sixth, PMRS argued that ROXYBOND's HAP study should have used the physical manipulation for reducing particle size that resulted in the highest release of the opioid and the highest plasma levels. FDA00018-20.

94. Last, PMRS argued that the results of ROXYBOND's HAP study indicate that the overall abuse potential of ROXYBOND remains significant despite the product's purported abuse-deterrent properties. FDA00020-22.

95. After 30 days passed with no response from FDA, PMRS sent Commissioner Gottlieb a letter to ensure his awareness of the PSA and to reiterate the urgency of PMRS's PSA.

96. After waiting months for a response, PMRS filed, *inter alia*, a petition for writ of mandamus seeking to compel FDA to respond promptly to PMRS's petition to stay the effective approval date of ROXYBOND. *See* 21 C.F.R. § 10.35(e) ("The Commissioner shall promptly review a petition for stay of action.").

E. FDA's Denial of PMRS's PSA on October 19, 2017.

97. On October 20, 2017, shortly before the Rule 16 Conference scheduled on PMRS's petition for writ of mandamus and other relief, counsel for FDA electronically transmitted a purported denial letter to PMRS's counsel, contending that the denial letter had been sent to PMRS on October 19, 2017 ("FDA's denial letter"). *See* FDA00372-379.

98. In its denial letter, FDA recognized the critical threat posed by this country's opioid epidemic. *Id.*

99. In its denial letter, FDA also acknowledged that PMRS raised "critical public health subject[s]" in its Citizen Petitions and PSA that are complex and, per FDA, warrant detailed inquiry. *Id.*

100. Yet FDA denied PMRS's petition to stay the effective approval date of ROXYBOND without offering any basis for continuing to approve opioids such as ROXYBOND during the pendency of FDA's review of the very issues that FDA itself has recognized are of critical importance to the public health, including a review of FDA's method of approving opioids.

101. Instead, FDA offers only a conclusory and unsupported assertion that PMRS failed to establish sound public policy grounds supporting a stay, despite recognizing the fundamental public policy and health issues raised in PMRS's Citizen Petitions and PSA.

102. Specifically, in its denial letter, FDA offered no explanation for its repeated approval of opioid drug products for the treatment of chronic pain, despite lacking substantial evidence to support the efficacy of these products in the chronic use setting.

103. FDA also offered no explanation for its failure to adhere to its own existing recommendations for laboratory-based *in vitro* manipulation and extraction studies when evaluating opioid drug products with potentially abuse-deterrent properties.

104. FDA offered no response to PMRS's arguments concerning FDA's troubling reliance on HAP studies, which are inherently flawed.

105. FDA offered no response to PMRS's position regarding the dangers inherent in failing to require postmarketing proof of abuse-deterrent labeling before permitting labeling for abuse-deterrence.

106. FDA did not explain how the approval of ROXYBOND with labeling claims pertaining to chronic use and abuse deterrence was in compliance with the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 301, *et seq.*, ("FDCA") and with the Agency's own regulations and guidance.

107. In particular, FDA did not explain the bases for its conclusion that the approval of ROXYBOND was supported by the requisite evidence of efficacy and safety.

108. There is no such evidence.

109. FDA also did not explain how the approval of ROXYBOND was consistent with the Agency's ADF Guidance, even though PMRS's PSA specifically highlighted several issues with the approval, such as the flawed particle size manipulation study and the failure of ROXYBOND's sponsor to use the product manipulation that caused the highest release of the opioid and the highest plasma levels in the HAP study.

110. The approval was not consistent with the Agency's ADF guidance.

111. In other words, FDA failed to respond to relevant arguments made by PMRS and failed to provide necessary findings and reasoning.

112. As FDA confirmed in its opposition to PMRS's motion to complete and supplement the record, FDA did not consider whether there is substantial evidence that opioids are effective in the treatment of chronic pain when FDA denied PMRS's PSA.

113. There is not substantial evidence that opioids are effective in the treatment of chronic pain.

114. There are no adequate and well-controlled studies showing that opioids are effective in the treatment of chronic pain.

115. There are no studies showing that abuse deterrent formulation has any impact in preventing addiction.

116. Moreover, FDA has not defined the legal standard for approval of so-called abuse-deterrent labeling for opioids, and its current "recommended" methodology is scientifically flawed, and, at best, results in labeling that is false and misleading.

117. In other words, FDA failed to respond to relevant arguments made by PMRS and failed to provide necessary findings and reasoning.

118. In its opposition to PMRS's motion to complete and supplement the administrative record, FDA did not address whether prescription opioids are safe and effective for the treatment of chronic pain when decided PMRS's PSA. *See* Dkt. 24 at 7.

119. In its opposition to PMRS's motion to complete and supplement the administrative record, FDA conceded that it did not address whether any previously approved

product upon which ROXYBOND's approval relies is safe and effective for use in the treatment of chronic pain. *Id.*

120. In its opposition to PMRS's motion to complete and supplement the administrative record, FDA conceded that it did not consider whether prescription opioids labeled as potentially abuse deterrent do, in fact, result in a meaningful reduction in misuse, abuse, addiction, overdose, and/or death. *Id.*

121. The Court's May 18, 2018, Order confirms that FDA did not consider whether it had comported with the predicate statutory and regulatory requirements for approving the previously approved products upon which ROXYBOND's approval relied in deciding PMRS's PSA. *See* Dkt. 30 at 4-5.

Respectfully submitted,

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A Member of The Firm

Dated: July 2, 2018

IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF PENNSYLVANIA

PHARMACEUTICAL MANUFACTURING RESEARCH SERVICES, INC., Plaintiff-Petitioner, v. UNITED STATES FOOD AND DRUG ADMINISTRATION, SCOTT GOTTLIEB, M.D., in his official capacity as the Commissioner of Food and Drugs, and his successors and assigns, and ERIC D. HARGAN, in his official capacity as the Acting Secretary of the United States Department of Health and Human Services, as well as his successors and assigns, Defendants.	**Civil Action No. 2:17-cv-4898-GJP** **PLAINTIFF PHARMACEUTICAL MANUFACTURING RESEARCH SERVICES, INC.'S INDEX OF EXHIBITS**

1. **EXHIBIT A**: Robert M. Califf, M.D., *et al.*, *A Proactive Response to Prescription Opioid Abuse*, 374 N. ENGL. J. MED. 1480, 1483-85 (2016), https://pdfs.semanticscholar.org/2dff/edbf472ceda90845ce25f24bbad308486218.pdf.

2. **EXHIBIT B**: Council of Economic Advisers, The Underestimated Cost of the Opioid Crisis, at 1 (November 2017), https://www.whitehouse.gov/sites/whitehouse.gov/files/images/The%20Underestimated%20Cost%20of%20the%20Opioid%20Crisis.pdf.

3. **EXHIBIT C**: Matrix Global Advisors, Health Care Costs from Opioid Abuse: A State-by-State Analysis, at 2-4 (Apr. 2015), https://drugfree.org/wp-content/uploads/2015/04/Matrix_OpioidAbuse_040415.pdf.

4. **EXHIBIT D**: DEA, Analysis of Overdose Deaths in Pennsylvania, 2016, at 5 (Jul. 2017), https://www.overdosefreepa.pitt.edu/wp-content/uploads/2017/07/DEA-Analysis-of-Overdose-Deaths-in-Pennsylvania-2016.pd_-1.pdf.

5. **EXHIBIT E**: Don Sapatkin, *Pa. leads nation in young men's overdose deaths, N.J. 4th*, The Philadelphia Inquirer (updated Nov. 20, 2015, 1:08 AM EST), http://www.philly.com/philly/health/addiction/20151120_Pa___N_J__lead_nation_in_young_men_s_overdose_deaths.html (last visited Oct. 31, 2017).

6. **EXHIBIT F**: Thomas R. Frieden & Debra Houry, Reducing the Risks of Relief — The CDC Opioid-Prescribing Guideline, 374 NEW ENG. J. MED. 1501, 1501 (2016), https://www.nejm.org/doi/full/10.1056/NEJMp1515917.

7. **EXHIBIT G**: FDA Response to Physicians for Responsible Opioid Prescribing (PROP) Citizen Petition (Sep. 10, 2013), at 10, https://www.regulations.gov/document?D=FDA-2012-P-0818-0793 (last visited Jun. 30, 2018).

8. **EXHIBIT H**: FDA, Transcript, Assessment of Analgesic Treatment of Chronic Pain: A Scientific Workshop (May 31, 2012) (statement of Janet Woodcock, M.D., Director, CDER), https://www.regulations.gov/document?D=FDA-2012-N-0067-0017.

9. **EXHIBIT I**: Medical Review (NDA 20977), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/209777Orig1s000MedR.pdf.

10. **EXHIBIT J**: Medical Review (NDA 21-011/AZ), Response to AE Letter (June 22, 2000), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/21-011_Roxicodone_Medr_P1.pdf.

11. **EXHIBIT K**: PERCODAN 2016 Labeling, https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/007337s049lbl.pdf.

12. **EXHIBIT L**: DESI Amended Classification Notice (PERCODAN, NDA 7337), 37 Fed. Reg. 26356, 26356 (Dec. 9, 1972), https://www.gpo.gov/fdsys/pkg/FR-1972-12-09/pdf/FR-1972-12-09.pdf.

13. **EXHIBIT M**: ROXYBOND 2017 Labeling, https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209777lbl.pdf.

14. **EXHIBIT N:** Jane C. Ballantyne, "Safe and effective when used as directed": the case of chronic use of opioid analgesics, 8 J Med Toxicol. 417 (2012), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3550253.

15. **EXHIBIT O:** Art Van Zee, *The Promotion and Marketing of OxyContin: Commercial Triumph, Public Health Tragedy*, 99 Am J Public Health 221 (2009), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2622774/.

16. **EXHIBIT P:** Center for Drug Evaluation and Research, Application Number 21-011, Administrative Documents, https://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/21-011_Roxicodone_Admindocs_P1.pdf (last visited Jun. 30, 2018)

17. **EXHIBIT Q:** Summary Review (NDA 20977), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/209777Orig1s000SumR.pdf (last visited Jun. 30, 2018).

18. **EXHIBIT R:** April 11, 2018 PMRS Response to FDA Notice.