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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, ALEX M. AZAR II, in his official capacity as the Secretary of the United States Department of Health and Human Services, as well as his successors and assigns, and JANET WOODCOCK, M.D., in her official capacity as the Director of the Center for Drug Evaluation and Research, as well as her successors and assigns, Defendants.	**Civil Action No.**

COMPLAINT FOR WRIT IN THE NATURE OF MANDAMUS RELIEF FOR THE ISSUANCE OF AN ORDER COMPELLING A HEARING UNDER 21 C.F.R § 314.200(g)(6)

Plaintiff-Petitioner Pharmaceutical Manufacturing Research Services, Inc. ("PMRS"), by and through its attorneys, McCarter & English, LLP, and for its Complaint for Writ in the nature of mandamus relief and for the issuance of an Order compelling the commence of a hearing or,

in the alternative, to compel FDA to respond to PMRS's request for a hearing, on PMRS's pending New Drug Application, NDA 209155 ("PMRS's NDA" or "NDA 209155"), pursuant to Section 505(c)(1)(B) of the Federal Food, Drug, and Cosmetic Act ("FDCA") and 21 C.F.R. § 314.200(g)(6) against the United States Food and Drug Administration ("FDA"), Scott Gottlieb, M.D., in his official capacity as the Commissioner of Food and Drugs and his successors and assigns, Alex M. Azar, II, in his official capacity as the Secretary of the United States Department of Health and Human Services ("HSS"), and his successors and assigns, and Janet Woodcock, M.D., in her official capacity as Director of the Center for Drug Evaluation and Research ("CDER"), and her successors and assigns, hereby alleges as follows:

INTRODUCTION

1. Plaintiff PMRS brings this action for declaratory relief and for a writ in the nature of mandamus due to the failure of the FDA, its Commissioner, Scott Gottlieb, M.D., and his successors and assigns, and the Director of FDA's CDER, Janet Woodcock, and her successors and assigns, to commence a hearing on FDA's proposal to refuse to approve NDA 209155 in the time provided by Section 505(c)(1)(B) of the FDCA.

2. Section 505(c)(1)(B) of the FDCA sets forth the timeline for conducting a hearing on FDA's refusal to approve an NDA.

3. According to section 505(c)(1)(B): "If the applicant elects to accept the opportunity for hearing by written request within thirty days after such notice, such hearing shall commence not more than ninety days after the expiration of such thirty days unless the Secretary and the applicant otherwise agree. Any such hearing shall thereafter be conducted on an expedited basis and the Secretary's order thereon shall be issued within ninety days after the date fixed by the Secretary for filing final briefs." 21 U.S.C. § 355(c)(1)(B).

4. The statutory timeline for commencing a hearing is implemented in Title 21 of FDA's regulations: "If the Commissioner grants a hearing, it will begin within 90 days after the expiration of the time for requesting the hearing unless the parties otherwise agree in the case of denial of approval . . ." 21 C.F.R. § 314.200(g)(5).

5. On February 13, 2018, FDA published in the Federal Register a proposal to refuse to approve NDA 209155 submitted by PMRS and a notice of opportunity for a hearing.

6. As required by statute, the notice provided PMRS with thirty days, *i.e.*, until March 15, 2018, to submit a request for a hearing.

7. On February 13, 2018, PMRS promptly filed a written notice of participation and request for a hearing.

8. Pursuant to section 505(c)(1)(B) of the FDCA and FDA's implementing regulations, upon expiration of the thirty-day period for requesting a hearing, FDA had ninety days to commence a hearing.

9. Thus, pursuant to statute, any hearing should have commenced on or before June 13, 2018.

10. On June 5, 2018, PMRS sent a letter to FDA's Office of the Commissioner ("OC") to remind it of the statutory deadline for commencing a hearing.

11. On June 13, 2018, FDA issued a proposed Order denying PMRS's request for a hearing regarding FDA's proposal to refuse to approve NDA 209155.

12. The proposed Order allowed PMRS to respond by August 10, 2018, with sufficient data, information, and other analyses to demonstrate that there is a genuine and substantial issue of fact justifying a hearing.

13. PMRS provided its response on August 9, 2018. ("August Hearing Request," attached hereto as Exhibit A.)

14. In that submission, which is incorporated by reference as if set forth fully herein, PMRS reiterated that there are genuine and substantial issues of fact requiring a hearing on FDA's proposed denial.

15. PMRS also argued that the Commissioner's decision to grant a hearing would be in the public interest.

16. Based on the data, information, and other analyses PMRS submitted, PMRS is legally entitled to a hearing on FDA's proposal to refuse to approve PMRS's NDA.

17. Specifically, pursuant to 21 C.F.R. § 314.200(g)(6), the Commissioner was required to grant a hearing on FDA's proposed denial of PMRS's hearing request under both standards set forth in the Agency's regulations.

18. Defendants' failure to commence the hearing on FDA's proposal to deny PMRS's pending NDA 209155 within the statutory period as required by Section 505(c)(1)(B) of the FDCA and by 21 C.F.R. § 314.200(g)(5) violates the Administrative Procedure Act ("APA"), 5 U.S.C. § 702, and the Mandamus Act, 28 U.S.C. § 1361.

19. FDA's unreasonable delay warrants this Court's involvement because it presents serious risks to the health and well-being of the American public in light of the ongoing and devastating opioid epidemic, as well as economic and competitive harm to PMRS.

20. PMRS seeks an order from this Court compelling FDA to commence the hearing on FDA's proposal to deny PMRS's NDA 209155 within thirty days (30) from the date of this Court's Order.

21. In the alternative, PMRS seeks an order from this Court compelling FDA to issue a final decision on PMRS's hearing request within 30 days from the date of this Court's Order.

JURISDICTION AND VENUE

22. This Court has subject matter jurisdiction over this action pursuant to: (a) 28 U.S.C. § 1331 ("[t]he district courts shall have original jurisdiction of all civil actions arising under the Constitution, laws, or treaties of the United States," *i.e.*, federal question jurisdiction); (b) 5 U.S.C. §§ 555(b), 702, 706(1) (judicial review provisions of the APA); and (c) 28 U.S.C. § 1361 ("[t]he district courts shall have original jurisdiction of any action in the nature of mandamus to compel an officer or employee of the United States or any agency thereof to perform a duty owed to the plaintiff.").

23. The declaratory relief requested in this action is authorized by 28 U.S.C. §§ 2201, 2202.

24. Venue is proper in the Eastern District of Pennsylvania pursuant to 28 U.S.C. § 1391(e)(1)(C), because that is the District in which Plaintiff-Petitioner PMRS resides.

PARTIES

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

26. 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.

27. 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.

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

29. FDA is headed by Defendant Scott Gottlieb, M.D., Commissioner of Food and Drugs, and operates under authority delegated by Congress and Defendant Alex M. Azar, II, Secretary of the U.S. Department of Health and Human Services ("HHS"), a federal agency headquartered in the District of Columbia.

30. Janet Woodcock, M.D., is the Director of CDER at FDA.

31. CDER is tasked with making sure that safe and effective drugs are available to improve the health of people in the United States.

32. CDER represents, on its website, that "Dr. Woodcock and her center: evaluate prescription and over the counter drugs before they can be sold and oversee their testing in clinical trials… ensure that drugs, both brand-name and generic, work correctly and that their health benefits outweigh their known risks [and] take action against unapproved, contaminated, or fraudulent drugs that are marketed illegally."

https://www.fda.gov/AboutFDA/CentersOffices/ucm193984.htm (last visited September 11, 2018).

33. Commissioner Gottlieb, Secretary Azar, Director Woodcock, 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.

FACTUAL BACKGROUND

34. FDA's regulations provide that the Commissioner will grant a hearing if (1) "there exists a genuine and substantial issue of fact" or (2) "the Commissioner concludes that a hearing would otherwise be in the public interest." 21 C.F.R. § 314.200(g)(6).

35. As established in its April 11, 2018, submission ("April Hearing Request" attached hereto as Exhibit B) and in its August 9, 2018, submission ("August Hearing Request"), PMRS' request for a hearing satisfies both of those regulatory standards.

A. PMRS Established that a Hearing is In the Public Interest.

36. PMRS established, pursuant to § 314.200(g)(6), that the Commissioner should grant its hearing request because a hearing on PMRS's NDA is in the public interest.

37. First, a hearing is in the public interest because it will promote the Agency's public health mission by further addressing the opioid epidemic.

38. The United States is enthralled in an opioid crisis that has long-since become a national emergency.

39. It is, therefore, difficult to imagine a more compelling public health justification for granting a hearing request than an NDA that was purposefully labeled to address the root cause of the opioid epidemic.

40. PMRS has argued that the Agency, in tandem with its other opioid-related initiatives, should take steps to directly target the root cause of the opioid epidemic: the labeling of opioids for the management of chronic pain despite a lack of substantial evidence to support that indication.

41. PMRS has also argued that FDA should re-assess its policy framework for evaluating purportedly abuse-deterrent opioids because eight years after the Agency's approval of reformulated OXYCONTIN (the only purportedly abuse-deterrent opioid to have gained market acceptance) there is still no credible evidence that any FDA-approved opioid formulation has resulted in a meaningful reduction in abuse.

42. As explained in its April Hearing Request, PMRS' proposed product embodies a novel approach to reducing the abuse potential of opioids—an approach that focuses more on the product's indication and recommended dosing than the hypothetical abuse-deterrent properties of its formulation.

43. Specifically, PMRS' proposed labeling is expected to reduce the abuse potential of its product because it adheres to the CDC's recommendations for prescribing opioids—recommendations that are supported by evidence that is both credible and reliable. This is a standard that does not exist in the marketplace.

44. Indeed, the role of CDC's recommendations in reducing opioid abuse stands independently of the fact that, as PMRS admits, neither its product nor any other opioid has post-market epidemiological data demonstrating the efficacy of its abuse-deterrent formulation.

45. As such, when determining whether to approve PMRS' NDA, FDA must consider PMRS' proposed labeling *in its entirety*, rather than focusing solely on any abuse-deterrent claims.

46. There also is a strong public interest in assuring that FDA acts in accordance with its governing laws and regulations.

47. Adhering to the metes and bounds of the Agency's authority—including the limitations Congress placed on that authority—is essential to maintaining public trust in the Agency's judgment that approved new drugs are safe and effective. FDA's disregard for these statutory requirements is the root cause of the epidemic.

48. As PMRS contends in its April Hearing Request, CDER's proposal to refuse to approve its NDA is unlawful because, in part, it is grounded in a lack of compliance with an

agency guidance document (FDA's Abuse-Deterrent Opioid Guidance), as opposed to a specific law or regulation.

49. Moreover, PMRS contends that FDA's Abuse-Deterrent Opioid Guidance is, itself, unlawful because its recommendations fail to comport with either the "substantial evidence" or the "false and misleading" standards articulated in the FDCA.

50. Additionally, as PMRS explained in its August Hearing Request, CDER's proposal to refuse to approve its NDA is unlawful because it is premised upon an alleged lack of compliance with a recently announced agency policy concerning the safety of excipients.

51. As explained in more detail below, FDA's decision to subject PMRS' NDA to this requirement is unlawful because the Agency's policy appears to (i) directly conflict with the Agency's governing laws and regulations; (ii) have been publicly articulated in an Advisory Committee presentation that post-dated PMRS's Complete Response Letter; and (iii) otherwise overturn FDA's longstanding approach to evaluating the safety of excipients without notice and comment rule-making.

52. Finally, a hearing is in the public interest because it would contribute to the public's understanding of FDA's process for approving opioid products and the evidentiary base that supports these approvals.

53. This, again, is essential to maintaining public trust in the Agency's judgment that the opioid products it approves are both safe and effective when used as labeled.

54. Public trust in the Agency's approval process is relevant not just to regulated industry, but also to all of the healthcare providers and patients who rely on the Agency's safety and effectiveness determinations to inform their prescribing and use of these products.

55. As discussed in its April Hearing Request, and as reiterated below, FDA's current position on the proposed labeling PMRS has requested—which again is the critical feature of its NDA—remains unclear because the Agency has provided conflicting signals on whether it will require PMRS to label its product for "chronic use" and with certain abuse-deterrent claims, even if PMRS were to object to such labeling.

56. Moreover, PMRS has attempted to gain clarity on these, and related questions, through other submissions outside of the hearing process.

57. In particular, PMRS has requested that FDA explain its decision to approve opioid products for the management of chronic pain, including the clinical evidence it relied on to support these approvals.

58. PMRS has similarly requested that FDA explain its decision to approve opioids with abuse-deterrent labeling, despite a lack of post-market epidemiology data to support these claims.

59. Accordingly, a hearing would afford both PMRS and the public at large with a better understanding of FDA's process for approving opioid products and the evidentiary base that supports these approvals.

B. PMRS Has Raised Precisely the Kind of Genuine and Substantial Issues of Fact that Require the Commissioner to Grant a Hearing.

60. There are genuine and substantial issues of fact concerning the review of NDA 209155, each of which requires the Commissioner to conduct a hearing.

61. In its August 9, 2018, submission, PMRS responded to the proposed Order from the Director of CDER to deny the request for a hearing and set forth the specific factual issues for which a hearing was required, including (1) so-called abuse-deterrent labeling; (2)

characterization of excipients for unintended uses; (3) exposure of PEG 3350; (4) intended and theoretical batch yields; and (5) the additional FDA-identified deficiencies.

62. For the reasons set forth in that submission and its April, 2018 submission, PMRS was entitled to a hearing on FDA's proposal to deny PMRS's NDA 209155 due to the factual issues raised therein.

C. PMRS is Being Penalized for Demanding that FDA Comply with Its Statutory Obligations Concerning the Approval of Opioids with Labeling for the Treatment of Chronic Pain.

63. FDA's treatment of PMRS's application confirms that PMRS is being penalized for demanding that FDA comply with its statutory obligations concerning the approval of opioids.

64. For approval, a drug must be determined to be safe and effective for use. 28 U.S.C. § 505(b).

65. An applicant must provide substantial evidence of efficacy for the conditions of use approved.

66. To provide substantial evidence, an applicant must conduct adequate and well-controlled studies. 21 U.S.C. 355(b).

67. For analgesic products, such as prescription opioid medications, FDA anticipates that at least two adequate and well-controlled studies will be needed to demonstrate efficacy.

68. 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, e.g.*, FDA, *Guidance for Industry—Analgesic Indications: Developing Drug and Biological Products*, at 2 (Feb. 2014), https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM384691.pdf (last visited Oct. 31, 2017).

69. 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.

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

70. 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." CDC, *Guideline for Prescribing Opioids for Chronic Pain*, at 34 (2016), https://www.cdc.gov/mmwr/volumes/65/rr/pdfs/rr6501e1.pdf (last visited Oct. 31, 2017).

71. 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." CDC, *Guideline for Prescribing Opioids for Chronic Pain*, at 13 (2016), https://www.cdc.gov/mmwr/volumes/65/rr/pdfs/rr6501e1.pdf (last visited Oct. 31, 2017).

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

73. 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." Robert M. Califf et al., *A Proactive Response to Prescription Opioid Abuse*, 374 New Eng. J. Med. at 1484.

74. Indeed, as FDA has previously conceded, the Agency "is not aware of adequate and well-controlled studies of opioid use longer than 12 weeks." 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 Oct. 31, 2017).

75. FDA has also conceded that, while the evidence base is strong for the efficacy of opioids for up to 12 weeks of treatment, their performance and liabilities 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." 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 Oct. 31, 2017).

76. 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." Robert M. Califf et al., *A Proactive Response to Prescription Opioid Abuse*, 374 New Eng. J. Med. at 1484.

77. In conducting its own due diligence, PMRS learned in addition to the current lack of evidence concerning opioid usage for treatment of chronic pain, there never was any substantial evidence of efficacy.

78. PMRS raised those issues in its pending Citizens Petitions to FDA.

79. Despite notifying FDA of those issues, and 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.

80. For example, and as is at issue in a parallel pending litigation involving PMRS, FDA improperly approved ROXYBOND with labeling for chronic use even though such use was not supported by new clinical studies demonstrating that ROXYBOND is an effective medication for the treatment of chronic pain.

81. Instead, ROXYBOND's approval relied upon FDA's prior findings of analgesic effectiveness for the reference product ROXICODONE.

82. ROXICODONE's approval, however, also is not based on new clinical studies demonstrating that the product is an effective medication for the treatment was of chronic pain.

83. Instead, ROXICODONE's approval relied upon FDA's prior findings of general analgesic effectiveness for the previously approved drug product PERCODAN.

84. 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.

85. 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).

86. Although FDA previously found PERCODAN to be an effective analgesic for the treatment of "moderate to moderately severe pain," its approval does not support the expanded chronic pain indication and higher dosing of oxycodone suggested in the ROXYBOND labeling.

87. 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." [ROXYBOND label] The ROXYBOND labeling also states that "Patients with chronic pain should have their dosage given on an **around-the-clock basis** to prevent the reoccurrence of pain rather than treating the pain after it has occurred." [ROXYBOND label] (emphasis added).

88. In contrast, neither the original nor current labeling for PERCODAN states that the product is intended for the treatment of chronic pain. PERCODAN's labeling also does not state that the product is intended to be administered on an "around-the-clock basis" for the prophylactic management of pain.

89. Indeed, the administrative history of PERCODAN indicates that no suitably controlled studies were submitted to support the effectiveness of PERCODAN for the treatment of *any* pain indication with the exception of postpartum pain.

90. Rather, PERCODAN's efficacy as a general analgesic was simply assumed because the product contained oxycodone.

91. Moreover, at the time of PERCODAN's approval in 1950, prescription opioids generally were not marketed or promoted to treat chronic pain. This situation changed in the mid-to-late 1990s with the approval of the prescription opioid OXYCONTIN which was

aggressively promoted for the treatment of chronic non–cancer-related pain. [Art Van Zee, The Promotion and Marketing of OxyContin: Commercial Triumph, Public Health Tragedy, x, Am J Public Health. 2009 February; 99(2): 221–227.]

92. Second, the current labeling for ROXYBOND—as well as that of its reference product ROXICODONE—states that the total daily dose of oxycodone typically should be between 20-90 mg (based on the 5 mg and 15 mg tablets). [ROXYBOND label] ("Initiate dosing with a range of 5 to 15 mg every 4 to 6 hours as needed for pain.")

93. However, ROXYBOND is also offered as a 30 mg tablet, which suggests a total daily dose of 120-180 mg of oxycodone.

94. In contrast, PERCODAN's labeling states that the total daily dose of oxycodone should typically be 20 mg, with the package insert acknowledging only that it may "occasionally be necessary to exceed the usual dosage recommended" in patients with severe pain or who are opioid-tolerant. [PERCODAN label] ("The usual dosage is one tablet [which contains ~5 mg of oxycodone] every 6 hours as needed for pain.").

95. 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.

96. 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.

97. Because PERCODAN is not an appropriate reference product for ROXYBOND (as currently labeled), 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.

98. In its parallel litigation, PMRS has confirmed that FDA's review documents on ROXYBOND are replete with the Agency's own acknowledgment that data supporting the efficacy of oxycodone as a single entity analgesic is lacking.

99. During its review of the original application submitted for ROXICODONE—the reference product for ROXYBOND—FDA found the application deficient because "No data to support effectiveness were included in the [application] as comparative studies included only . . . **unapproved** 5 mg [oxycodone] tablets." 2000 Memo. (emphasis added).

100. FDA concluded that the 5-mg oxycodone tablets used in the comparative studies submitted in the original ROXICODONE application could not be relied on to demonstrate efficacy because, while marketed, the product had never been approved and was "neither a grandfathered nor a DESI drug."

101. 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." 1999 Memo (emphasis added).

102. 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).**" See September 16, 1999 Memorandum from Cynthia McCormick, Center for Drug Evaluation and Research, Application Number 21-011, Roxicodone Administrative Documents (emphasis added).

103. 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).

104. 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]**." 1999 Memo (emphasis added).

105. The "preferable alternative" to demonstrating efficacy based on PERCODAN was, according to FDA, for ROXICODONE's sponsor to "provide [new] clinical trials for any of the [single-entity oxycodone] IR dosage forms (5 mg, 15 mg and 30 mg)." 1999 Memo.

106. In sum, separate and apart from the lack of evidence to support use for chronic pain specifically, the aforementioned regulatory history raises questions about whether it was proper for FDA to rely on PERCODAN (a combination drug product) to establish the efficacy of single-entity IR oxycodone products such as ROXICODONE and, by extension, ROXYBOND.

107. PMRS's own research and development of its NDA 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.

108. 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.[1]

109. In its interim responses, FDA conceded that PMRS has raised complex issues of public policy and welfare.

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

110. Yet FDA proceeded to approve ROXYBOND, despite those threshold statutory issues.

111. PMRS filed a PSA on May 11, 2017.

112. FDA denied that PSA and, 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.

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

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

115. FDA's treatment of ROXYBOND creates a rigid and harmful dichotomy, wherein FDA delays responding substantively to PMRS's Citizen Petitions that raise fundamental questions about FDA's role in facilitating the opioid epidemic, but then rushes to approve yet another opioid product with chronic use labeling and purported abuse-deterrent properties, despite the scientific community's recognition that the evidence needed to support such claims is lacking, all while effectively blocking PMRS's request for a hearing on its NDA, per the regulations.

116. PMRS promptly moved to stay the effective approval date of ROXYBOND during the pendency of FDA's review of its Citizen Petitions.

117. When FDA failed to respond to that Petition, arguing that it did not have to rule on PMRS's motion to stay, PMRS filed suit in this Court against FDA under the APA to compel FDA's response.

118. Thereafter, FDA provided a response, denying PMRS's Petition.

119. PMRS then filed a second action, currently pending under Civil Action Number 2:17-cv-4898-GJP, to reverse FDA's denial as arbitrary, capricious, and contrary to the law based upon FDA's failure to consider the predicate issue of whether it had satisfied its statutory obligation of showing that there is substantial evidence that opioids are effective for the treatment of chronic pain.

120. Recently, Raeford Brown, Jr., M.D., the Chair of FDA's Advisory Committee on Analgesic and Anesthetic Drug Products ("FDA's AADP") and a consultant to the Centers for Disease Control and Prevention on Opioids and their Prescribing Characteristics in the United States, submitted an amicus brief in PMRS's pending litigation that confirms that FDA does not have substantial evidence of efficacy of opioids with labeling for use in the treatment of chronic pain. A copy of Dr. Brown's submission is attached hereto as Exhibit C.

121. Dr. Brown, who was Chair of FDA's Advisory Committee when it voted to approve ROXYBOND, is in a unique position to confirm the deeply troubling issues with FDA's approval process for opioids.

122. In his submission to the Court in the parallel matter, Dr. Brown explains in his submission to the Court that FDA never had substantial evidence of efficacy of opioids with labeling for chronic use. (Brown Letter, attached hereto as Exhibit C at 2.)

123. Dr. Brown opines that:

> The guidance by the FDA that is included with all prescription drugs lists chronic pain as an indication for their use. This

> guidance is required by statute to be based on reasonable clinical and biological science, **yet there is currently no evidence which provides background for the continued labeling, nor was there ever any substantial evidence.** There have been countless assertions of the efficacy of the agents. Unfortunately, assertions carry little scientific weight. Thus, the continued insistence by the Agency that opioids are indicated for the treatment of chronic pain sends a message to patients and clinicians that it is appropriate to prescribe these agents when the risks of prescribing outweigh the apparent benefits. **This action by the Agency is directly related to inappropriate prescribing of opioids to patients, to their tolerance to these agents, and to long-term use or addiction to opioids. The balance of risks and benefits in prescribing opioids for long-term use for noncancer pain is evident. There is precious little benefit while the risk is substantial.**

(*Id.* (emphasis added).)

124. Dr. Brown further opines in his submission that to date, there is a "lack of available scientific evidence that chronic pain, that is pain which is prolonged beyond twelve weeks, can be safely treated with the continuous opioid administration." (Brown Letter at 1, attached hereto as Exhibit A.)

125. Thus, Dr. Brown's submission confirms that FDA never secured substantial evidence of efficacy before allowing opioids to go to market with labeling for chronic use.

126. Dr. Brown opines in his submission that the prevalence in the market of opioids with labeling for chronic use "has been an important driver of the drug crisis" in this country. (*Id.* at 2.)

127. He also opines that FDA's efforts to course correct by pursing abuse deterrent labeling has failed.

128. As Dr. Brown explains in his submission to the Court, there is no evidence that abuse deterrent formulation prevents addiction.

129. Instead, as Dr. Brown explains, "the Agency was never able to provide a rational argument for the use of this formulation and pressed the committee to review and make decisions based on data that was incomplete and that had been presented to obtain a given outcome." (*Id.* at 2.)

130. Dr. Brown further confirms that "[a]n examination of the current literature suggests that, not only have these medications failed to reduce the use of opioids, but that they have likely played an outsized role in increasing the mortality rate from opioid use by forcing users to switch to illicit drugs which are less expensive and are nearly always adulterated with other dangerous agents." (*Id.* at 2-3.)

131. In sum, Dr. Brown's submission confirms that FDA's approval of opioids with labeling for chronic use occurred despite the lack of statutorily-mandated substantial evidence of efficacy.

132. FDA, therefore, has no statutory authority to approve opioids such as ROXYBOND with labeling for chronic use.

133. 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 and there is no evidence that opioids should be on the market with labeling for chronic use.

134. In turn, for the purposes of this litigation, FDA's failure to conduct a hearing on PMRS's NDA, which seeks to use the correct acute use labeling, is deeply troubling, patently unfair and seemingly punitive.

CLAIM FOR RELIEF

135. The foregoing allegations are incorporated by reference and repeated as though set forth in full herein.

136. Defendants' failure to commence the hearing on FDA's proposal to deny PMRS's pending NDA 209155 within the statutory period as required by Section 505(c)(1)(B) of the FFDCA and by 21 C.F.R. § 314.200(g)(5) and (6) violates the Administrative Procedure Act ("APA"), 5 U.S.C. § 702, and the Mandamus Act, 28 U.S.C. § 1361.

137. Requiring PMRS to wait any longer for the hearing on its NDA to commence would be unjust, wasteful, and significantly harmful to the public health, because absent PMRS is being precluded from bringing its product to market with correct labeling, while other, mislabeled and dangerous opioids are permitted to proceed to market.

138. Defendants' failure to commence the hearing or, in the alternative, to respond to PMRS' request for a hearing, represents "agency action" that has been "unreasonably delayed," and therefore PMRS is entitled to an order from this Court pursuant to the APA and in the nature of mandamus compelling Defendants to commence the hearing within 30 days of the date of this Court's Order. 5 U.S.C. § 706(1); 28 U.S.C. § 1361.

WHEREFORE, Plaintiff-Petitioner PMRS prays that this Court enter an Order:

a. Declaring that Defendants have unreasonably delayed in commencing a hearing on PMRS's NDA and that such unreasonable delay is a violation of the Administrative Procedure Act and applicable FDA regulations;

b. Compelling Defendants, by injunction and/or writ in the nature of mandamus, to commence the hearing within 30 days of the entry of this Court's Order or, in the alternative, to respond to PMRS's request for a hearing by a date certain; and

c. Awarding PMRS attorneys' fees, reasonable expenses incurred in connection with this action, and such other relief as this Court deems equitable, just, and proper under the circumstances.

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Dated: September 11, 2018

By: _____
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