or prevents the use of plasma in settings where freezers and other support equipment are unavailable (*e.g.* battlefields, remote locations, and other austere settings) and may lead to delayed administration. Dried plasma (such as freeze-dried or spray-dried plasma) offers the potential to address these challenges by providing a product that is stable at ambient temperatures and can be rapidly reconstituted and transfused.

Recent clinical studies have demonstrated promising efficacy and safety of dried plasma, particularly in military applications, and dried plasma products are available for limited use in Germany, South Africa, and France. This guidance is intended to assist manufacturers, sponsors, and applicants developing dried plasma products intended for transfusion in order to facilitate the availability of safe and effective dried plasma products in the United States.

This draft guidance is being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115). The draft guidance, when finalized, will represent the current thinking of FDA on considerations for the development of dried plasma products intended for transfusion. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. This guidance is not subject to Executive Order 12866.

II. Paperwork Reduction Act of 1995

This draft guidance refers to previously approved collections of information subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501–3520). The collections of information in 21 CFR part 211 have been approved under OMB control number 0910–0139; the collections of information in 21 CFR part 312 have been approved under OMB control number 0910–0014; the collections of information in 21 CFR part 601 have been approved under OMB control number 0910–0338; the collections of information in 21 CFR part 610 have been approved under OMB control numbers 0910–0116, 0910–0139, and 0910–0338; the collections of information in 21 CFR part 630 have been approved under OMB control number 0910–0116; the collections of information in 21 CFR part 640 have been approved under OMB control number 0910–0116; the collections of information in 21 CFR part 812 have been approved under OMB control number 0910–0078; and the collections of information in 21 CFR part 814 have been approved under OMB control number 0910–0231.

III. Electronic Access

Persons with access to the internet may obtain the draft guidance at either *https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm* or *https://www.regulations.gov.*

Dated: October 25, 2018.

Leslie Kux,

Associate Commissioner for Policy.

[FR Doc. 2018–23637 Filed 10–29–18; 8:45 am]

BILLING CODE 4164–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2018–N–0188]

Denial of Hearing Request Regarding Proposal To Refuse To Approve a New Drug Application for Oxycodone Hydrochloride Immediate-Release Abuse-Deterrent Formulation, Oral Capsules, 5 Milligrams, 15 Milligrams, and 30 Milligrams; Order Refusing Approval

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Chief Scientist is denying a request for a hearing regarding the proposal by the Center for Drug Evaluation and Research (CDER) of the Food and Drug Administration (FDA or Agency) to refuse to approve a new drug application submitted by Pharmaceutical Manufacturing Research Services, Inc. (PMRS) for oxycodone hydrochloride (HCl) immediate-release (IR) capsules, 5 milligrams (mg), 15 mg, and 30 mg in its present form. The Chief Scientist denies approval.

DATES: The order is applicable October 30, 2018.

FOR FURTHER INFORMATION CONTACT: Nathan R. Sabel, Office of Scientific Integrity, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 1, Rm. 4206, Silver Spring, MD 20993, 301–796–8588.

SUPPLEMENTARY INFORMATION:

I. Procedural Background

PMRS submitted new drug application (NDA) 209155 for oxycodone HCl IR capsules, 5 mg, 15 mg, and 30 mg, under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(b)(2)), relying in part on the Agency's previous findings of safety and effectiveness for ROXICODONE (oxycodone HCl IR tablets (NDA 021011)) (Ref. 1).

PMRS's product contains excipients, including a dye blend, that have solubility in common solvents, including water and ethanol, similar to the solubility of the active pharmaceutical ingredient (API). PMRS contends that a solution prepared from its product for subcutaneous or intravenous injection will look relatively ''impure'' compared to a solution prepared from Roxicodone and will have a dark, opaque, ''contaminated-looking'' appearance, providing both a ''visual deterrent'' and a ''chemical deterrent'' to abuse by injection (Refs. 2 and 3).[1] PMRS provided in vitro data intended to show that a solution prepared for injection would have these qualities but provided no data or literature supporting the conclusion that people who inject opioids would, in fact, be deterred from injecting such a solution (Ref. 2).

PMRS also provided in vitro data intended to demonstrate that its product would be more difficult to grind into particle sizes suitable for snorting compared to ROXICODONE but provided no data from studies in human subjects to evaluate the pharmacokinetic or pharmacodynamic properties of the product following abuse via the nasal route (Ref. 1).[2] Nonetheless, PMRS proposed labeling for its product representing that it has abuse-deterrent properties (Ref. 4).

On November 16, 2017, CDER issued a complete response letter to PMRS under § 314.110(a) (21 CFR 314.110(a)) stating that the NDA could not be

[1] With respect to the purported ''chemical deterrent'' aspect of its product, we note that PMRS's claims that its product resists physical and chemical ''extraction'' appear to rest on a misunderstanding of how that term is used in the context of abuse-deterrent opioids. PMRS appears to be using the term ''extraction'' to mean that it is difficult to separate the API from the excipients in solution, not that it is difficult to prepare a solution that contains the API. In fact, PMRS's data show that the oxycodone in its formulation can be readily extracted in commonly available solvents into a solution physically suitable for injection. These data show that more of the API could be extracted from oxycodone HCl IR capsules (approximately 98 percent of the API) than from ROXICODONE (approximately 90–91 percent) in both small and medium volume extraction and at ambient and high temperatures (Refs. 1 and 2).

[2] While PMRS initially intended for the product to confer resistance to grinding to particle sizes suitable for snorting (Ref. 7), PMRS has conceded, based on the results of its testing, that the formulation should not be considered to have this property. See Ref. 2 at 12–13 (''Because of the decrease in particle size distribution after grinding as the drug product ages, resistance to grinding cannot be considered as one of the characteristics of [PMRS' product]'').

approved in its present form, describing the specific deficiencies, and, where possible, recommending ways PMRS might remedy these deficiencies (Ref. 5). The deficiencies cited include the following:

(1) The application in its present form is not approvable with the proposed labeling describing abuse-deterrent properties, for multiple reasons. In particular, (a) the oxycodone in the formulation can be readily extracted in commonly available solvents into a solution suitable for injection; (b) there were insufficient data showing the presence of excipients (including dye) in the formulation can be expected to deter abuse by injection; (c) the data submitted were insufficient to show the product was meaningfully resistant to manipulation for misuse or abuse; and (d) there were not data submitted, including data from pharmacokinetic and human abuse liability studies, fully characterizing the product's abuse potential by all relevant routes of abuse. Also, the data submitted were not sufficient to rule out the possibility that the proposed formulation could result in a greater proportion of abuse by injection of PMRS's product compared to a conventional oxycodone IR formulation. Abuse by injection carries greater risk of overdose and transmission of infectious disease than abuse by other routes.

(2) The safety and purity of the excipients intended (but not shown) to confer abuse-deterrent properties were not adequately characterized, either by the intended oral route of use or by expected routes of abuse, including injection.

(3) An overall evaluation of elemental impurities in the final formulation and a risk assessment for each heavy metal (taking into consideration the maximum daily dose) were not provided.

(4) The application did not fully comply with the patent certification requirements applicable to applications submitted under section 505(b)(2) of the FD&C Act.

The complete response letter describes additional deficiencies relating to the chemistry, manufacturing, and controls (CMCs) and current good manufacturing practice requirements that CDER determined precluded approval of the application in its present form (Ref. 5). The complete response letter also noted that satisfactory resolution of objectionable inspection observations was required before the application could be approved (Ref. 5).

In response to the complete response letter, on November 17, 2017, PMRS submitted a request for an opportunity for hearing under § 314.110(b)(3) on whether there are grounds under section 505(d) of the FD&C Act for denying approval of the NDA.

On February 13, 2018, FDA published a notice of opportunity for a hearing (NOOH) setting forth CDER's proposal to refuse to approve PMRS's NDA for oxycodone HCl IR capsules in 5-mg, 15-mg, and 30-mg strengths (83 FR 6196). The NOOH stated that, for the reasons described above and others described in the complete response letter, notice is given to PMRS and to all other interested persons that FDA proposes to issue an order refusing to approve the NDA because the application fails to meet the criteria for approval under section 505(d) of the FD&C Act, including that: (1) PMRS has not provided sufficient data to show that the product would be safe (section 505(d)(1)); (2) PMRS has not shown that the methods used in, and the facilities and controls used for, the manufacture, processing, or packing of the product are adequate to preserve its identity, strength, quality, and purity (section 505(d)(3)); and (3) the labeling PMRS proposed for the product is false or misleading (section 505(d)(7)).

PMRS submitted a request for a hearing on February 15, 2018. PMRS also submitted data, information, and analysis in support of its hearing request on April 13, 2018 (April Submission).[3] CDER submitted a proposed order on June 13, 2018, and PMRS submitted a Response to CDER's Proposed Order on August 9, 2018 (August Submission), consistent with regulations at § 314.200(g)(3) (21 CFR 314.200(g)(3)), affording the hearing requestor 60 days to respond to a proposed order.

II. Statutory and Regulatory Framework Regarding 21 CFR Part 12 Hearings

Under § 12.24(a)(2) (21 CFR 12.24(a)(2)), the Agency reviews a hearing request to determine whether a hearing has been justified. FDA has the authority to deny a hearing when it appears from the hearing request that there are no material disputes of fact. See *Costle* v. *Pacific Legal Found.,* 445 U.S. 198, 214 (1980) (a party seeking a hearing is required to meet a ''threshold burden of tendering evidence suggesting the need for a hearing''), *reh'g denied,* 446 U.S. 947 (1980), citing *Weinberger* v. *Hynson, Westcott & Dunning, Inc.,* 412 U.S. 609, 620–21 (1973); *Pineapple Growers Ass'n* v. *FDA,* 673 F.2d 1083, 1085–86 (9th Cir. 1982) (holding that no hearing is necessary unless ''material issues of fact'' have been raised).

In determining whether there are material issues of fact suitable for a hearing, FDA considers the specific criteria set out in § 12.24(b) and grants a hearing only if the material submitted in support of the request shows the following: (1) There is a genuine and substantial factual issue for resolution at a hearing; a hearing will not be granted on issues of policy or law; [4] (2) the factual issue can be resolved by available and specifically identified reliable evidence; a hearing will not be granted on the basis of mere allegations or denials or general descriptions of positions and contentions; (3) the data and information submitted, if established at a hearing, would be adequate to justify resolution of the factual issue in the way sought by the requestor; a hearing will be denied if the Agency concludes that the data and information submitted are insufficient to justify the factual determination urged, even if accurate; [5] (4) resolution of the factual issue in the way sought by the person is adequate to justify the action requested; a hearing will not be granted on factual issues that are not determinative with respect to the action requested (*e.g.,* if the Agency concludes that the action would be the same even if the factual issue were resolved in the way sought); [6] (5) the action requested is

[3] Although timely filed, PMRS did not submit the data, information, and factual analysis in the required format (*e.g.,* the submission lacks a statement signed by the person responsible for such submission that it includes in full all studies and information as required) (§ 314.200(d)(3)). The Chief Scientist has nevertheless reviewed PMRS's April Submission in its entirety.

[4] See also *Georgia Pacific Corp.* v. *U.S. EPA,* 671 F.2d 1235, 1241 (9th Cir. 1982) (finding that a party's argument that a hearing is necessary to ''sharpen the issues'' or to ''fully develop the facts'' is not sufficient to justify a hearing); *Citizens for Allegan County, Inc.* v. *FPC,* 414 F.2d 1125, 1128 (D.C. Cir. 1969) (finding that ''no evidentiary hearing is required where there is no dispute on the facts and the agency proceeding involves only a question of law.''); and *Sun Oil Co.* v. *FPC,* 256 F.2d 233, 240 (5th Cir. 1958), *cert. denied,* 358 U.S. 872 (1958).

[5] See also *John D. Copanos & Sons, Inc. and Kanasco, Ltd.* v. *FDA,* 854 F.2d 510, 522 (D.C. Cir. 1988) (''The mere existence of some alleged factual dispute between the parties will not defeat an otherwise properly supported motion for summary judgment; the requirement is that there be no *genuine* issue of *material* fact . . . Only disputes over facts that might affect the outcome of the suit under the governing law will properly preclude the entry of summary judgment. Factual disputes that are irrelevant or unnecessary will not be counted.'') (emphasis in original), quoting *Anderson* v. *Liberty Lobby, Inc.,* 477 U.S. 242, 247–248 (1986) and *Hynson,* 412 U.S. at 620.

[6] See also *Hynson,* 412 U.S. at 621 (1973) and *Dyestuffs & Chemicals, Inc.* v. *Flemming,* 271 F.2d 281, 286 (8th Cir. 1959) (''Where the objections stated and the issues raised thereby are, even if true, legally insufficient, their effect is a nullity and no objections have been stated. Congress did not intend the governmental agencies created by it to

Continued

not inconsistent with any provision in the FD&C Act or any FDA regulation; and (6) the requirements in other applicable regulations, *e.g.,* 21 CFR 10.20, 12.21, 12.22, and 314.200, and in the NOOH are met. Similarly, § 314.200(g) provides that a person requesting a hearing ''may not rely upon allegations or denials but is required to set forth specific facts showing that there is a genuine and substantial issue of fact that requires a hearing with respect to a particular drug product specified in the request for hearing.''

III. Analysis

Following review of the administrative record related to this proceeding, the Chief Scientist [7] finds that PMRS has not raised a genuine and substantial issue of fact justifying a hearing regarding CDER's proposal to refuse to approve the NDA in its present form.[8] As further explained below, the Chief Scientist finds that a hearing would not otherwise be in the public interest. Accordingly, the Chief Scientist denies PMRS's hearing request under §§ 12.24(b) and 314.200(g) and orders approval denied under section 505(d) of the FD&C Act for PMRS's NDA in its present form.

A. PMRS's Request for a Hearing Is Denied Because No Genuine and Substantial Issue of Fact Exists Regarding the Lack of Sufficient, Reliable Evidence Supporting PMRS's Proposed Labeling for Abuse-Deterrent Properties

Among other bases for proposing to deny PMRS's NDA, the NOOH cites the requirement that FDA deny approval to applications that propose labeling that is false or misleading in any particular (see section 505(d)(7) of the FD&C Act; 21 CFR 314.125(b)(6)). On this basis, the November 16, 2017, complete response letter explained that the NDA in its current form is not approvable with the proposed labeling describing abuse-deterrent properties. PMRS proposed labeling that includes multiple statements that the product has properties that make it more difficult to manipulate for purposes of abuse and misuse than a conventional formulation (Ref. 6). These statements include the assertion that the product ''is formulated with inactive ingredients that make the capsule more difficult to manipulate for misuse and abuse'' and that ''the results of this testing demonstrated that [the product] capsules, in comparison to Roxicodone tablets, have increased resistance to physical and chemical extraction.'' (Ref. 6).[9]

Specifically, the complete response letter explained that PMRS submitted ''[n]o data . . . to support the proposed hypothesis that the presence of excipients or dye in the solution would create a deterrence to intravenous abuse'' (Ref. 5). Generally, PMRS's hypothesis is that commonly used methods of preparing a solution for injection, if applied to its product, will result in a solution that will look ''visually unappealing'' compared to a solution prepared from Roxicodone, and will have a dark, opaque, ''contaminated-looking'' appearance that will serve as a ''visual deterrent'' to abuse (Ref. 2). PMRS's NDA provided in vitro data intended to show that a solution prepared for injection would have such an appearance (Refs. 2 and 3).[10]

As CDER informed PMRS during the application process, CDER considered this in vitro data unable to prove that PMRS's hypothesis is correct that individuals would actually be deterred by the appearance of a solution prepared from this formulation (Ref. 8). Although a solution prepared from PMRS's product may appear a certain way based on the in vitro data provided, PMRS has produced no scientific data or information to establish that people who inject opioids would be less likely to do so because of this appearance or based upon knowledge that the solution contains other components of the drug product in addition to the API. To demonstrate that this formulation deters abuse, and thus to support the proposed labeling for abuse-deterrent properties, CDER asked PMRS to provide evidence sufficient to prove that people who abuse opioids by injection would be deterred from doing so based on the solution's appearance.[11]

Critically, however, PMRS's NDA and subsequent submissions in this proceeding contain no such data or information on this critical question, either from PMRS's studies of its own product or from any potentially relevant scientific literature. In lieu of scientifically valid evidence for the proposition that appearance deters abuse, PMRS simply reiterates how the solution appears. PMRS states, variously, that the ''dark, significant color is visually unappealing for potential intravenous abuse'' (Ref. 2); that ''PMRS considers this visual deterrent effective in classifying drug products as abuse deterrent'' (id.); that ''[t]he use of an FD&C dye was considered a deterrent to abuse as it

perform useless or unfruitful tasks.''), *cert. denied,* 362 U.S. 911 (1960).

[7] Under FDA Staff Manual Guide 1410.21, the Chief Scientist is authorized to perform all delegable functions of the Commissioner of Food and Drugs. (See FDA Staff Manual Guide 1410.21 ¶ 1.B.7).

[8] PMRS suggests that it has an absolute statutory right to a hearing on whether its NDA is approvable under section 505(c)(1)(B) of the FD&C Act without regard to whether it can satisfy the criteria for a hearing set forth in FDA's regulations, including the requirement that a person requesting a hearing must demonstrate with data and analysis that there is a genuine and substantial issue of fact that requires a hearing (April Submission at 6–7). PMRS is incorrect. FDA's duly issued summary judgment procedures have been consistently upheld and are fully compatible with section 505(c)(1)(B) of the FD&C Act. ''It is well established that the statutory grant of a public hearing is not absolute'' (*Community Nutrition Inst.* v. *Young,* 773 F.2d 1356, 1364 (D.C. Cir. 1985)). FDA has the authority to deny a hearing when it appears from the submission of the party requesting a hearing that no substantial issue of fact is in dispute (*Pineapple Growers Ass'n,* 673 F.2d at 1085–86; *Hynson,* 412 U.S. at 621; *Hess & Clark, Inc.* v. *FDA,* 495 F.2d 975, 983 (D.C. Cir. 1974)).

[9] In its latest submission, PMRS appears to propose revising its NDA labeling to include the statement ''Oxycodone HCl IR ADF capsules should be prescribed knowing meaningful abuse-deterrent properties have not been proven,'' among other labeling adjustments (August Submission at 5). First, PMRS cannot adjust the content of the NDA that is the subject of this hearing process in the middle of the process itself. Among other reasons, the question this proceeding seeks to resolve is not whether PMRS might formulate an NDA that might address some of the deficiencies cited in the NOOH. Rather, this process seeks to determine whether the application PMRS submitted to CDER for review should be denied approval as CDER proposes. PMRS may not change the substance of that application during this proceeding. Second, given that the ''ADF'' abbreviation of the product name PMRS retains in this revised language stands for ''Abuse Deterrent Formulation,'' it is difficult to see how this change, even if permissible, would remove the concern that is the primary focus of this order: that PMRS's labeling represents that its product possesses abuse-deterrent properties when the presence of such properties is not supported by substantial and reliable evidence. Consistent with the regulations governing this 21 CFR part 12 proceeding, this order evaluates PMRS's NDA as it was evaluated by CDER and not as PMRS might seek to modify that application now. If PMRS wishes to seek Agency review of a different NDA at this juncture, the appropriate avenue would be to submit a new application through the standard Agency process.

[10] According to CDER's review, there remain some questions concerning whether a solution extracted from PMRS's formulation would consistently have the dark or opaque appearance observed in PMRS's in vitro data. The appearance of an extracted solution of the product may vary, depending on the solvent used in extraction and filtering methods employed by experienced abusers. However, for the purposes of this order, the Chief Scientist assumes that the solution extracted from PMRS's formulation appears as a dark, opaque solution.

[11] CDER informed PMRS of the need for such evidence prior to PMRS's submission of the NDA:

''At this time, we are not aware of data that support a deterrent effect based on the presence of a dye in a formulation intended to be abuse-deterrent. Provide evidence that supports the concept that the incorporation of a dye into a formulation imparts abuse-deterrent effects to that formulation. A hypothetical argument that the presence of a dye will provide an abuse-deterrent effect is not sufficient to support labeling.'' (Ref. 8).

provides a visual deterrent once introduced to aqueous solution'' (id.); that ''the ready solubility of the excipients matching the solubility profile of the API . . . maximiz[es] deterrence by rendering [the product] less attractive or rewarding for injection due to the inability to isolate the API from the inactive ingredients for injection'' (Ref. 9); and that ''it was very important that excipients for this formulation have same [solubility] in order to provide a chemical deterrent for abuse'' (Ref. 2).[12] Despite these assertions and the in vitro data related to how the product looks in solution, PMRS has offered no evidence to establish that opioid-abusers will be deterred by the color or appearance of a solution prepared from PMRS's formulation.

PMRS has also failed to offer evidence to establish its proposed conclusion related to another deficiency cited in the complete response letter (Ref. 5), specifically, PMRS's failure to establish that its product formulation deters abuse by snorting. Despite CDER's requests that human testing be conducted to establish whether this formulation deters abuse by snorting (see Refs. 5 and 8), PMRS declined to conduct such testing or to provide any other information to show that its product functions to deter abuse by snorting. Without human testing, or other appropriate data and information, it is not possible to evaluate whether PMRS's formulation has properties that render it more or less likely to be snorted.[13] If the product were in fact less likely to be snorted, the product could result in shifting the pathway of abuse from snorting to injection. This shift would *increase* the product's overall risks associated with abuse compared to a conventional formulation, both because abuse by injection of any opioid carries additional risks particular to that route of abuse (Ref. 10) and because abuse by injection of PMRS's product in particular carries unknown additional risks associated with injection of the co-extracted excipients.[14]

The Chief Scientist concludes that PMRS has not created a genuine and substantial issue of fact justifying a hearing on this issue. As CDER informed PMRS during the review process and in the complete response letter, PMRS has not provided evidence that demonstrate its product deters abuse. Despite requesting a factual hearing and offering in vitro data intended to demonstrate how its product looks in solution, PMRS has not provided sufficient and reliable data or information that creates a genuine and substantial dispute of fact with respect to whether the appearance of such a solution deters abuse in the manner PMRS proposes to describe in its labeling. PMRS may have submitted evidence to show what the product looks like when prepared for injection but PMRS has not provided no clinical evidence—or indeed any evidence—that this appearance will deter abuse as PMRS's NDA represents in its proposed labeling. In addition, PMRS has failed to provide sufficient evidence to establish that the product formulation deters abuse by snorting. As a result, there exists no contested factual issue with respect to the information available to demonstrate whether PMRS's formulation possesses abuse-deterrent properties. Accordingly, the Chief Scientist denies PMRS's request for a factual hearing on this issue under §§ 12.24(b) and 314.200(g) because there exists no genuine and substantial issue of fact that would require such a hearing to resolve.

B. PMRS's NDA Proposes Labeling That Is False and Misleading Under Section 505(d)(7) of the FD&C Act and Is Therefore Appropriately Denied Approval

Having found that that is no genuine and substantial question of fact with respect to whether PMRS's proposed labeling is false or misleading, the Chief Scientist also finds that the Agency must therefore issue an order refusing to approve PMRS's NDA in its present form under section 505(d)(7) of the FD&C Act.

FDA makes approval decisions, including decisions regarding the content of FDA-approved prescription drug labeling, based on a comprehensive scientific evaluation of the available data and information, allowing only information for which there is a scientific basis to be included.[15] As discussed above, no evidence establishes the proposition that this formulation has the abuse-deterrent properties PMRS proposes to include in its product labeling.[16] The absence of such evidence in support of PMRS's assertions is particularly problematic in light of the novel and highly speculative nature of PMRS's abuse-deterrence hypothesis. It is well understood that people suffering from opioid use disorder—particularly people who abuse opioids by injection—routinely take extraordinary risks in connection with their opioid abuse. The individuals who abuse opioids by injection are known to be undeterred by such serious risks as disease transmission (including HIV and hepatitis C) associated with needle-sharing, injection-site infections, overdose, and even death (Ref. 10). Certain ''street'' opioids, such as black tar heroin, are commonly administered by injection despite their contaminated appearance (Ref. 11) and despite the real risks associated with the unknown composition and purity of such products (including, but not limited to, the presence of contaminants).

Against this backdrop, PMRS's unsupported assertions and in vitro data are insufficient to demonstrate that its product formulation will deter abuse. Given the lack of data establishing the effect of PMRS's formulation on its risks of abuse compared to a conventional formulation, the labeling statements PMRS has proposed suggesting that sufficient and reliable evidence exists and establishes that PMRS's formulation deters abuse would be false and misleading. Thus, the proposed labeling

[12] We note that PMRS provided some data and information regarding its particular choice of dye blend, arguing that the blend it selected was ''the most visually deterring'' of the colors evaluated ''as it resulted in a dark, opaque, 'contaminated-looking' solution'' (Ref. 2 at page 4). As this order discusses, this data does not constitute sufficient evidence for the proposition that people who inject opioids can reasonably be expected to be ''visually deterred'' from doing so based on the appearance of the solution prepared for injection.

[13] As previously noted, PMRS intended for its formulation to confer resistance to grinding (for the purpose of snorting) but ultimately conceded that the product has not been shown to have this property. See supra footnote 2.

[14] In June 2017 FDA sought withdrawal from the market of OPANA ER (oxymorphone HCl ER tablets (NDA 21610)) based on similar concerns (Ref. 12). Specifically, FDA requested that OPANA ER be withdrawn from the market after review of postmarket data showed a significant shift in the route of abuse from nasal to injection following the product's reformulation. The reformulated product had been intended to deter abuse by injection and snorting. Injection abuse of reformulated OPANA ER has been associated with serious adverse events, including numerous cases of thrombotic microangiopathy which are thought to have been related to injection of the excipients included to deter abuse (Refs. 12 and 13).

[15] See, *e.g.,* 21 CFR 201.56(a)(1) (providing that the labeling of prescription drugs must contain a summary of the essential scientific information needed for the safe and effective use of the drug), 21 CFR 201.56(a)(2) (providing that the labeling must be informative and accurate and neither promotional in tone nor false or misleading in any particular and that labeling must be updated when new information becomes available that causes the labeling to become inaccurate, false, or misleading), and 21 CFR 201.56(a)(3) (providing that labeling must be based whenever possible on data derived from human experience).

[16] As noted previously, PMRS's claims that its product resists physical and chemical ''extraction'' appear to rest on a misunderstanding of how that term is used in the context of abuse-deterrent opioids. See supra footnote 1.

includes false and misleading statements suggesting that PMRS's product is expected to be safer than a conventional formulation with respect to the risks of abuse when this conclusion remains unproven.[17] Accordingly, the Chief Scientist has determined that PMRS has not submitted data or information that can support a conclusion that its product would deter abuse by injection and that PMRS's proposed labeling is false and misleading under section 505(d)(7) in the absence of such evidence. As a result, the Chief Scientist accepts CDER's proposal to refuse approval for PMRS's NDA in its present form.

C. PMRS's Legal and Policy Arguments Are Unavailing

Instead of providing data and information addressing the absence of genuine and substantial issues of fact discussed in the previous sections, the PMRS's submissions consists largely of legal and policy objections to FDA's approach to evaluating, labeling, and approving opioids, as well as requests for the Agency to take specific actions regarding other drug products premised on PMRS's proposed alternative policies regarding opioids. These legal and policy arguments do not raise a genuine and substantial issue of fact justifying a hearing. See § 12.24(b)(1) (''A hearing will not be granted on issues of policy or law.'').[18] Furthermore, a hearing will not be granted on the issue of whether FDA should take regulatory actions regarding other drug products which are not the subject of the NOOH.[19] Accordingly, this order does not address the merits of FDA's policies regarding abuse-deterrent opioids or PMRS's objections to those policies, except as they apply to the question of whether PMRS has raised a genuine and substantial issue of fact which precludes CDER's proposal to refuse to approve PMRS's NDA.[20] Instead, the Chief Scientist's order addresses only those aspects of the PMRS submissions that are at least potentially relevant to the question of whether PMRS has submitted data, information, or analysis that raises a genuine and substantial issue of fact justifying a hearing on the issue of whether PMRS's proposed abuse-deterrent labeling claims are false or misleading.

PMRS argues that CDER incorrectly proposed refusing to approve its NDA with the proposed abuse-deterrent labeling because CDER applied what PMRS considers the flawed approach to the evaluation and labeling of abuse-deterrent products contained in FDA's 2015 guidance for industry, ''Abuse-Deterrent Opioids—Evaluation and Labeling'' (Ref. 14) (the Guidance). Specifically, PMRS argues that the guidance's emphasis on premarket studies (*i.e.,* laboratory studies and human testing) is scientifically invalid and that FDA should only approve abuse-deterrent formulations with abuse-deterrent labeling claims based on post-market epidemiological data. PMRS contends that data from premarket studies of abuse deterrence cannot constitute ''substantial evidence'' that a product deters abuse and therefore results in abuse-deterrent labeling claims that are false and misleading (April Submission at 2–5). PMRS further argues that CDER improperly treated compliance with the guidance approach as a requirement for approval of abuse-deterrent labeling, rather than merely as a set of recommendations, in violation of the Administrative Procedure Act (APA) (April Submission at 5–7). The Chief Scientist finds these arguments unconvincing and not relevant to the matter at hand.

First, PMRS makes a policy argument that FDA, by following the approach described in the Guidance, routinely approves abuse-deterrent labeling claims that are too strong or overly broad based on premarket data. But this argument does not raise an issue of fact regarding the approvability of an NDA for a product bearing a labeling claim that PMRS characterizes as a ''more appropriately limited claim about abuse deterrence'' (April Submission at 2). As stated above, PMRS has not presented data, information, or analysis that support a conclusion that its product is approvable with *its own proposed labeling,* rendering the question of whether ''broader labeling statements'' (April Submission at 2) should be withheld until supported by post-market epidemiological data irrelevant for purposes of this order.[21] Even in its August submission, PMRS continues to suggest that its product should be labeled as possessing abuse-deterrent properties, even naming its product ''ADF'' or Abuse Deterrent Formulation, while simultaneously arguing that no evidence can demonstrate such properties pre-market (August Submission at 5).[22] If PMRS is correct that such properties cannot be established pre-market, then labeling its product with abuse-deterrent properties becomes even more transparently false and misleading. PMRS cannot have it both ways without admitting that their proposed labeling lacks a scientific basis. Further, even if FDA were to agree with PMRS that only labeling claims of the type proposed by PMRS should be approved based on premarket studies, this policy change would not alter the conclusion that PMRS has not raised a genuine and substantial issue of fact justifying a hearing regarding CDER's proposal to refuse to approve PMRS's NDA with the labeling described in the NDA.[23]

The Chief Scientist finds PMRS's APA claim similarly irrelevant to the question of whether a hearing should be granted. PMRS contends that, by recommending that PMRS follow the

[17] During the review process, PMRS proposed that its labeling include the following disclaimers: ''Abuse of TRADENAME by injection, as well as by the oral and nasal routes, is still possible,'' and ''there is no clinical evidence that TRADENAME has a reduced abuse liability compared to immediate-release oxycodone'' (Ref. 6). These disclaimers do not render PMRS's other abuse-deterrent labeling statements any less false and misleading. For example, the first disclaimer implies that the product has abuse-deterrent properties, while stating that these properties do not render the product abuse-proof. The second disclaimer conveys an assessment of the product's abuse-deterrent properties is not based on data from human studies but continues to suggest that the product possesses these (unproven) properties. In the context of the other labeling PMRS proposes related to abuse-deterrence, these disclaimers, if anything, render the NDA's proposed labeling even more misleading.

[18] Courts have uniformly recognized that an administrative hearing need not be held to resolve questions of law or policy (see *Citizens for Allegan County,* 414 F.2d 1125 (D.C. Cir. 1969); *Sun Oil Co.* v. *FPC,* 256 F.2d 233, 240 (5th Cir.), cert denied, 358 U.S. 872 (1958)).

[19] § 314.200(g)(8) (''A request for a hearing, and any subsequent grant or denial of a hearing, applies only to the drug products named in [the NOOH]'').

[20] Similarly, this order does not address PMRS's arguments that do not go to the specific deficiencies cited in the complete response letter and the NOOH, such as its argument that its product, as well as other opioid products, should not bear labeling consistent with chronic use and instead should only be labeled for management of acute pain.

[21] For similar reasons, the Chief Scientist does not address the merits of PMRS's legal argument that application of the approach described in the Guidance raises concerns under the First Amendment. PMRS contends that ''[i]t cannot be that an Agency can compel an applicant to forego a more limited truthful and non-misleading claim and to instead seek broader labeling claims that an applicant finds objectionable'' (April Submission at 4, footnote 4). Given that PMRS has not presented data, information, or analysis that support a conclusion that its product is approvable with what PMRS characterizes as more limited claims regarding abuse-deterrence, PMRS's First Amendment objections to broader labeling claims are not relevant to this proceeding.

[22] See supra footnotes 6 and 16.

[23] We note that the Guidance was developed after considerable deliberation by the Agency and after thorough consideration of stakeholder comments expressed at public meetings and submitted to the docket. If PMRS wants to provide further input on the Guidance, there is already a mechanism in place for PMRS to do so (see § 10.115(f)). A hearing on CDER's proposal to refuse to approve PMRS's NDA, however, is not the proper forum for effecting changes to FDA policy. See § 12.24(b)(1).

approach to evaluating abuse-deterrent opioids described in the Guidance, and by referring to the guidance in the complete response letter and other documents, CDER ''effectively converted a nonbinding guidance document into a requirement for abuse-deterrent labeling that has the force and effect of the law'' (April Submission at 7). But challenging FDA's recommended approach for study design to measure abuse-deterrent effectiveness pre-market is immaterial to the proposal to refuse PMRS's specific NDA because PMRS has provided no evidence—either of the type FDA recommended or otherwise—that this formulation deters abuse. As a result and as discussed in the previous section, PMRS's proposed labeling remains false and misleading because it represents abuse-deterrent properties for a formulation that has not been shown to actually possess those properties.

In sum, the Chief Scientist concludes that PMRS has raised no legal or policy argument that alters the determinations discussed in the previous sections.

D. A Hearing is not Otherwise in the Public Interest

In its August Submission, PMRS argues that a Part 12 hearing would be ''otherwise in the public interest'' within the meaning of § 314.200(g)(6) in order to resolve broader policy issues related to opioid abuse. The Chief Scientist disagrees and finds in her discretion that a Part 12 hearing on this NDA would not otherwise be in the public interest.

As discussed above, PMRS's submissions raise arguments relevant to FDA's regulation of opioid products and to the crisis of opioid abuse, generally. For example, PMRS argues that the ''emphasis on so-called abuse-deterrent formulations and labeling in response to the opioid epidemic has resulted in the market entry of additional misbranded products'' and that ''[s]uch false and misleading labeling serves only to confuse prescribers and patients about what the product is and . . . is not'' (April Submission at 4). In its submissions, PMRS also requests that FDA take specific regulatory action regarding several other specific opioid products.

The Agency continues to take a variety of steps to address the public health crisis created by opioid abuse and the resulting addiction and death. For example, in May 2017, the Commissioner of Food and Drugs (the Commissioner) announced the establishment of an Opioid Policy Steering Committee to explore and develop additional approaches or strategies FDA could deploy to combat the opioid crisis.[24] FDA has also held public hearings on topics relating to opioid abuse, including to receive stakeholder input on how FDA might, under its Risk Evaluation and Mitigation Strategy (REMS) authority, improve the safe use of opioid analgesics by curbing overprescribing to decrease the occurrence of new addictions and limit misuse and abuse of opioid analgesics.[25]

The Agency is also working to enhance prescriber and patient awareness of the safe use of opioids. In 2017, FDA notified holders of approved applications for IR opioid analgesics of the Agency's determination that a REMS is necessary for IR opioid analgesics to ensure that the benefits of these drugs continue to outweigh the risks. Under this new policy, the IR opioid analgesics that are intended to be used in the outpatient setting will be subject to the same REMS requirements as the Extended-Release/Long-Acting opioid analgesics.

In addition, the Agency is undertaking a study to improve its understanding of prescriber beliefs relating to use of opioid products with abuse-deterrent properties.[26] The Agency is evaluating currently-used nomenclature for such products, including by surveying doctors to better understand how they perceive these terms and to assess the clinical understanding that has developed around products with labeling for abuse-deterrent properties. Further, FDA is continuously monitoring the safety of approved opioid products based on post-market information, including through a focus on improving post-market data collection in this area.

As these examples show, the Agency is working to address the crisis of opioid addiction and abuse and recognizes the importance of seeking public comment and participation relevant to FDA's opioid-related policies. However, the Chief Scientist does not believe that a Part 12 hearing on the approvability of PMRS's NDA is an appropriate forum to address such concerns and finds in her discretion that such a hearing would not be in the public interest.

E. Additional Issues Not Decided by This Order

As described above, the Chief Scientist has determined that PMRS has not raised a genuine and substantial issue of fact that would warrant a hearing and that PMRS's proposed labeling containing abuse-deterrent representations would be false and misleading under section 505(d)(7) of the FD&C Act. Although the complete response letter and NOOH describe additional deficiencies in PMRS's NDA, it is not necessary to address these issues in this order because, even if resolved in PMRS's favor, PMRS's NDA would still be refused approval in its present form under section 505(d)(7) of the FD&C Act.[27]

IV. Findings and Order

For the reasons described above, the Chief Scientist finds that PMRS has not raised any genuine and substantial issue of fact that would justify a hearing (see §§ 12.24(b)(1) and 314.200(g)(1)). Accordingly, PMRS's request for a hearing is denied. The record conclusively shows that the approval criteria set forth in section 505(d)(7) of the FD&C Act have not been met. Therefore, under section 505(d) of the FD&C Act of the FD&C Act, the Chief Scientist hereby denies approval to PMRS's NDA in its present form.

V. References

The following references marked with an asterisk (*) are on display in the Dockets Management Staff (HFA–305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, and are available for reviewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; they are also available electronically at *https://www.regulations.gov.* The reference without an asterisk is not on public display at *https://www.regulations.gov* because it has copyright restriction. References without asterisks are available for viewing only at the Dockets Management Staff. FDA has verified the website addresses, as of the date this document publishes in the **Federal Register**, but websites are subject to change over time.

* 1. Clinical Review, Cross-Discipline Deputy Director Review and Summary Division Director Review, NDA 209155.
* 2. ''Module 3 Quality, 3.2.P.2.2 Drug Product,'' PMRS Inc., NDA 209155.
* 3. ''Module 2 Common Technical Document Summaries,'' PMRS, NDA 209155.

[24] See 82 FR 58572 (December 13, 2017).

[25] Id.

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

[27] ''A hearing will be denied if the Commissioner concludes that the data and information submitted are insufficient to justify the factual determination urged even if accurate.'' § 12.24(b)(3). Furthermore, ''[a] hearing will not be granted on factual issues that are not determinative with respect to the action requested, *e.g.,* if the Commissioner concludes that the action would be the same even if the factual issue were resolved in the way sought[.]'' § 12.24(b)(4).

* 4. Proposed labeling for oxycodone HCl IR capsules, PMRS, NDA 209155 (Dec. 2017).
* 5. Complete Response letter, NDA 209155 (November 16, 2017).
* 6. ''Filing Communication Responses,'' PMRS, NDA 209155.
* 7. ''Request for Priority Review Designation,'' PMRS, NDA 209155.
* 8. ''Memorandum of Meeting Minutes'' for Type B, Pre-NDA, July 11, 2016 teleconference (August, 8, 2016).
* 9. ''NDA 209155 CMC Information Request 5–25–17,'' PMRS, NDA 209155.
* 10. Centers for Disease Control, ''Integrated Prevention Services for HIV Infection, Viral Hepatitis, Sexually Transmitted Diseases, and Tuberculosis for Persons Who Use Drugs Illicitly: Summary Guidance From the CDC and the U.S. Department of Health and Human Services,'' *Morbidity and Mortality Weekly Report,* vol. 61, pp. 1–40, 2012.
* 11. National Institute on Drug Abuse, ''What is heroin and how is it used?'', available at *https://www.drugabuse.gov/publications/research-reports/heroin/what-heroin* (accessed June 13, 2018).
* 12. FDA News Release, ''FDA requests removal of Opana ER for risks related to abuse'' (June 8, 2017), available at *https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm562401.htm.*
13. Hunt, R. et al., ''A Mechanistic Investigation of Thrombotic Microangiopathy Associated with IV Abuse of Opana ER,'' *Blood,* Feb. 16, 2017.
* 14. FDA Guidance for Industry ''Abuse-Deterrent Opioids—Evaluation and Labeling,'' available at *https://www.fda.gov/downloads/Drugs/Guidances/UCM334743.pdf.*

Dated: October 25, 2018.

Denise Hinton,

Chief Scientist.

[FR Doc. 2018–23710 Filed 10–29–18; 8:45 am]

BILLING CODE 4164–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Health Resources and Services Administration

Meeting of the National Advisory Council on Nurse Education and Practice

AGENCY: Health Resources and Services Administration (HRSA), Department of Health and Human Services (HHS).

ACTION: Notice.

SUMMARY: The National Advisory Council on Nurse Education and Practice (NACNEP or the Council) has scheduled a public meeting. Information about NACNEP and the agenda for this meeting can be found on the NACNEP website at *https://www.hrsa.gov/advisory-committees/nursing/index.html.*

DATES: November 19, 2018, 8:30 a.m.–4:15 p.m. ET.

ADDRESSES: This meeting will be held by teleconference and webinar. The conference call-in number is 1–888–455–0640; passcode: HRSA COUNCIL. The webinar link is *https://hrsa.connectsolutions.com/nacnep/.*

FOR FURTHER INFORMATION CONTACT: Tracy L. Gray, MBA, MS, RN, Division of Nursing and Public Health, Bureau of Health Workforce, HRSA, 5600 Fishers Lane, 11N112, Rockville, Maryland 20857; 301–443–3346; or *DScott1@hrsa.gov.*

SUPPLEMENTARY INFORMATION: NACNEP provides advice and recommendations to the Secretary of Health and Human Services (Secretary) and the U.S. Congress on policy matters arising in the administration of Title VIII of the Public Health Service (PHS) Act, as amended, including the range of issues relating to nurse supply, education, and practice improvements. NACNEP provides an annual report to the Secretary and Congress describing the activities of NACNEP, including findings and recommendations made by NACNEP concerning the activities under this title.

During the November 19, 2018, meeting, NACNEP will continue discussing areas where nursing can take the lead in the transition of the health care system to value-based care through improvements to nurse education and practice, to advance the development of its 15th Report. In addition, the members will discuss strategic priorities and future directions for the Council and discuss possible topics for its 16th Report. Agenda items are subject to change as priorities dictate. Refer to the NACNEP website for any updated information concerning the meeting.

Members of the public will have the opportunity to provide comments. Public participants may submit written statements in advance of the scheduled meeting. Oral comments will be honored in the order they are requested and may be limited as time allows. Requests to make oral comments or provide written statements to NACNEP should be sent to Ms. Tracy L. Gray, Designated Federal Official, using the contact information above at least 3 business days prior to the meeting.

Amy P. McNulty,

Acting Director, Division of the Executive Secretariat.

[FR Doc. 2018–23685 Filed 10–29–18; 8:45 am]

BILLING CODE 4165–15–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Government-Owned Inventions; Availability for Licensing

AGENCY: National Institutes of Health, HHS.

ACTION: Notice.

SUMMARY: The invention listed below is jointly owned by an agency of the U.S. Government with Pontificia Universidad Catolica de Chile and is available for licensing to achieve expeditious commercialization of results of federally-funded research and development. Foreign patent applications are filed on selected inventions to extend market coverage for companies and may also be available for licensing.

FOR FURTHER INFORMATION CONTACT: Licensing information and copies of the U.S. patent application listed below may be obtained by communicating with Ami Gadhia, JD, LL.M., CLP, Technology Transfer and Patenting Specialist, National Center for Advancing Translational Sciences, NIH, 9800 Medical Center Drive, Rockville, MD 20850, Phone: 301–217–6098, or email *ami.gadhia@nih.gov.* A signed Confidential Disclosure Agreement will be required to receive copies of unpublished patent applications.

SUPPLEMENTARY INFORMATION: Technology description follows.

c-Abl Tyrosine Kinase Inhibitory Compounds and Methods of Manufacture and Use

Description of Technology

The invention includes compounds that inhibit c-Abl tyrosine kinase, and methods of making them which include administering (i) a therapeutically effective amount of the compound or a stereoisomer, tautomer, pharmaceutically acceptable salt, solvate, or prodrug thereof; or (ii) a therapeutically effective amount of the pharmaceutical compositions to a patient with the disease which involves c-Abl tyrosine kinase, including the overexpression of it. In some embodiments, the compound inhibits c-Abl tyrosine kinase by binding to an allosteric site of the c-Abl tyrosine kinase. In some embodiments, the compound binds to a myristate pocket of the c-Abl tyrosine kinase.

This technology is available for licensing for commercial development in accordance with 35 U.S.C. 209 and 37 CFR part 404, as well as for further