United States Court of Appeals

FOR THE DISTRICT OF COLUMBIA CIRCUIT

Argued December 3, 2019 Decided May 1, 2020

No. 18-1335

PHARMACEUTICAL MANUFACTURING RESEARCH SERVICES, INC.,
PETITIONER

v.

FOOD & DRUG ADMINISTRATION, ET AL.,
RESPONDENTS

On Petition for Review of a Final Order
of the United States Food & Drug Administration

Elizabeth P. Papez argued the cause and filed the briefs for petitioner.

Sarah Carroll, Attorney, U.S. Department of Justice, argued the cause for respondents. With her on the brief were *Scott R. McIntosh*, Attorney, *Robert P. Charrow*, General Counsel, U.S. Department of Health and Human Services, and *AnnaMarie Kempic*, Deputy Chief Counsel, Litigation.

Before: HENDERSON, WILKINS, and RAO, *Circuit Judges*.

Opinion for the Court filed by *Circuit Judge* RAO.

RAO, *Circuit Judge*: Before bringing a new drug to the market, a pharmaceutical manufacturer must demonstrate to the Food and Drug Administration that the drug is safe, effective, and works as described. Here, petitioner Pharmaceutical Manufacturing Research Services ("PMRS") sought approval to market a prescription opioid drug that PMRS claims will be less prone to abuse by patients. The FDA denied the application, finding that PMRS's draft label was false and misleading because there was no evidence that the drug in fact possessed abuse deterrent properties. The agency also denied PMRS's request for a hearing regarding approval of its application. PMRS challenges both determinations under the Administrative Procedure Act. We conclude that the FDA's decision to deny the application was reasonable and consistent with law and that its decision to deny PMRS's request for a hearing was not an abuse of discretion. We therefore deny the petition for review.

I.

In recent years, as the prescription opioid crisis gripping the United States has worsened, the pharmaceutical industry has placed increasing emphasis on developing new formulations of opioid medications designed to deter abuse. Such "abuse-deterrent formulations" possess physical or chemical properties that are intended to make it more difficult for patients to take advantage of "the known or expected routes of [opioid] abuse, such as crushing in order to snort or dissolving in order to inject." FDA, *Abuse-Deterrent Opioid Analgesics* (last updated June 11, 2019), https://go.usa.gov/xyKd7.

As for any new drug, a manufacturer seeking FDA approval to market a prescription opioid with a label describing the drug as "abuse deterrent" must establish,

among other things, "substantial evidence that the drug will have the effect it purports … to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof," 21 U.S.C. § 355(d)(5), and that the proposed label is not "false or misleading in any particular," *id.* § 355(d)(7). "Substantial evidence" is defined in the Food, Drug, and Cosmetic Act ("FDCA") as "adequate and well-controlled investigations, including clinical investigations, by experts …, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have … in the … proposed labeling thereof." *Id.* § 355(d).

With respect to abuse deterrent opioids, the FDA has elaborated on the FDCA's general evidentiary standards for new drugs. In 2015, the agency published a guidance document that purports to "explain[] FDA's current thinking" about the types of clinical studies "that should be conducted to demonstrate that a given formulation [of an opioid] has abuse-deterrent properties," "how those studies should be performed and evaluated[,] … and their implications in product labeling." FDA, *Abuse-Deterrent Opioids—Evaluation and Labeling: Guidance for Industry* 1 (Apr. 2015) ("2015 Guidance"), https://www.fda.gov/media/84819/download. The 2015 Guidance sets out three categories of "premarket studies" that the FDA states will be "appropriate" "[i]n most cases … to obtain a full and scientifically rigorous understanding of the impact of a technology or technologies on a product's abuse potential." *Id.* at 5.

Petitioner PMRS is a privately owned pharmaceutical company that produces a range of oral solid and liquid drugs. In January 2017, PMRS submitted a new drug application ("NDA") seeking FDA approval for an immediate-release formulation of oxycodone that PMRS claimed to have abuse

deterrent properties. In its application, PMRS proposed to include "ADF," short for "Abuse Deterrent Formulation," in the product name and to include various statements in the label describing the drug's abuse deterrent chemical and physical properties. The proposed label read in relevant part:

> TRADENAME is formulated with inactive ingredients that make the capsule more difficult to manipulate for misuse and abuse. …
>
> In vitro physical and chemical manipulation studies … demonstrated that TRADENAME capsules … have increased resistance to physical and chemical extraction [relative to a previously approved opioid, Roxicodone].
>
> There is no clinical evidence that TRADENAME has a reduced abuse liability compared to immediate-release oxycodone.
>
> Abuse of TRADENAME by injection, as well as by the oral and nasal routes, is still possible.

J.A. 66–67. The label's claim regarding "inactive ingredients" referred in part to the inclusion of a dye blend that was intended to give a solution prepared from the drug a "dark, opaque," "contaminated" appearance. J.A. 412. PMRS claimed this would "create a visual deterrent to abuse" by intravenous injection. J.A. 412.

In November 2017, the FDA sent PMRS a complete response letter explaining that its NDA could not be approved in its current form. *See* 21 C.F.R. § 314.110(a) (describing

FDA process for complete response letters). The letter identified numerous deficiencies in the NDA that would bar approval under governing law. Most relevant to this appeal, the FDA stated it could not conclude based on the evidence that PMRS's drug possessed the abuse deterrent properties described in the proposed label. Among other things, the agency found that PMRS had failed to submit evidence supporting its hypothesis that the inclusion of dye in the formulation would deter intravenous abuse. Moreover, studies showed that PMRS's drug was "easily manipulated to create a solution suitable for abuse by the [intravenous] route." J.A. 54. The FDA recommended that PMRS address these deficiencies by reformulating its product with properties expected to deter intravenous and nasal[1] abuse and by conducting Category 1, 2, and 3 studies (as defined in the 2015 Guidance) to support the abuse deterrent labeling claims.[2]

Rather than attempt to remedy these deficiencies and resubmit its NDA, PMRS requested a hearing regarding approval of its application. In a series of submissions to the FDA over the ensuing months, PMRS asserted that its

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[1] PMRS initially claimed that its product possessed properties expected to deter nasal abuse, but later abandoned that claim, conceding that there was insufficient evidence to support it.

[2] The complete response letter also identified several other statutory grounds on which to deny the application, including that PMRS had not provided sufficient data to show that the drug's formulation was safe, *see* 21 U.S.C. § 355(d)(1), or that "the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug are [adequate] to preserve its identity, strength, quality, and purity," *id.* § 355(d)(3). The FDA recommended steps PMRS could take to address those deficiencies.

proposed label reflected a "novel approach to reducing [opioid] abuse potential" by focusing on product "indication and recommended dosing [more] than the hypothetical abuse-deterrent properties of [the drug's] formulation." J.A. 890. In other words, PMRS did not submit additional evidence to support the label's statements concerning the drug's physical and chemical properties. Instead, the company insisted that its product carried less potential for abuse because it would be indicated only for acute, rather than long-term, pain management, and because the label would recommend a maximum daily dosage that was lower than similar opioids already on the market. According to PMRS, the acute pain indication coupled with lower dosing recommendations would make its drug "the safest labeled opioid" on the market. J.A. 575. PMRS also argued that the FDA's approach to abuse deterrence, as laid out in the 2015 Guidance, was "misleading, unscientific, and dangerous," J.A. 575, and that a hearing was needed to address the flaws in the agency's approach.

In June 2018, the FDA sent PMRS a draft order proposing denial of PMRS's application and hearing request. The draft order reiterated the deficiencies identified in the complete response letter and explained that PMRS had failed to identify a genuine factual issue that would justify a hearing. The agency described numerous statutory grounds on which to deny the NDA, including that PMRS's proposed label was false and misleading given the lack of scientific support for the label's statements about abuse deterrence.

Two months after receiving the proposed order, PMRS filed a response in which it suggested modifying the draft label to read, as relevant here:

> Oxycodone HC1 IR ADF capsule is formulated with inactive ingredients

> intended to make the capsule more difficult to manipulate for misuse and/or abuse. Postmarketing epidemiology evidence is required to demonstrate meaningful abuse-deterrent properties. **Oxycodone HC1 IR ADF capsules should be prescribed knowing meaningful abuse-deterrent properties have not been proven.**

J.A. 893 (emphasis in original).

The FDA issued a final order denying PMRS's request for a hearing and refusing to approve its NDA in October 2018. *See* 83 Fed. Reg. 54,598 (Oct. 30, 2018) ("Denial Order"). The agency's decision rested exclusively on its finding that PMRS's proposed label was false or misleading under the FDCA. *Id.* at 54,601–02 (citing 21 U.S.C. § 355(d)(7)). As the FDA explained, PMRS failed to provide evidence supporting its claim that the drug "has properties that make it more difficult to manipulate for purposes of abuse and misuse than a conventional formulation." *Id.* at 54,600. Given the complete "lack of sufficient, reliable evidence supporting PMRS's proposed labeling for abuse-deterrent properties," the FDA found that a hearing was not required because there was no "genuine and substantial issue of fact" as to whether the NDA was approvable in its present form. *Id.* (capitalization altered). The FDA declined to address additional statutory deficiencies in the NDA because "even if resolved in PMRS's favor, PMRS's NDA would still be refused approval in its present form" due to the false and misleading label. *Id.* at 54,603.

The FDA acknowledged that PMRS had recently proposed modifying the label to state that "meaningful abuse-deterrent properties have not been proven," but refused to

consider revisions to the NDA made months after PMRS requested a hearing. *Id.* at 54,600 n.9. The agency also noted that in any event the proposed revisions did not appear to address its concerns about the false or misleading label, as PMRS still sought to include "ADF" in the product name, conveying that the product had an "abuse deterrent formulation." *Id.* Similarly, the FDA declined to address other arguments raised by PMRS that did not relate to the specific concerns about the label cited in the complete response letter—including PMRS's claim that its product would deter abuse because it would "only be labeled for management of acute [rather than chronic] pain." *Id.* at 54,602 n.20.

Finally, the FDA concluded a hearing was not needed to address PMRS's "legal and policy objections to FDA's approach to evaluating, labeling, and approving opioids." *Id.* at 54,602. The FDA explained that these issues had no bearing on the approvability of PMRS's application, and that the agency had determined a hearing was not otherwise in the public interest, *see* 21 C.F.R. § 314.200(g)(6), because a hearing on a specific new drug application was not the appropriate forum to address broader concerns about the agency's approach to the opioid epidemic. 83 Fed. Reg. at 54,602–03.

PMRS timely filed a petition for review pursuant to 21 U.S.C. § 355(h), which permits applicants to appeal an FDA order denying approval of a new drug application to this court.

II.

PMRS challenges the denial of the NDA on two grounds: first, that a false or misleading label is not a sufficient statutory ground on which to deny a new drug application; and second, that denying the application based on the draft

label was arbitrary and capricious and contrary to law. We explain in turn why each APA challenge fails.

A.

As a preliminary matter, PMRS asserts that the FDA's refusal to approve its application was contrary to law because the FDCA does not permit the agency to deny an NDA solely on the basis of a false or misleading label.

As with all questions of statutory interpretation, we start with the text. *See, e.g.*, *Ross v. Blake*, 136 S. Ct. 1850, 1856 (2016). The FDCA provides first that the FDA "shall … approve [a new drug] application if [the agency] finds that *none* of the grounds for denying approval specified in subsection (d) applies." 21 U.S.C. § 355(c)(1)(A) (emphasis added). Subsection (d), in turn, provides that the FDA "s*hall* issue an order refusing to approve [an] application" if it finds that one of seven grounds—enumerated in subsections (d)(1) through (d)(7)—exists. *Id.* § 355(d) (emphasis added). Subsection (d)(7) covers situations in which the FDA concludes, "based on a fair evaluation of all material facts," that the applicant's proposed labeling "is false or misleading in any particular." *Id.* § 355(d)(7). Together, these provisions indicate that any of the seven grounds for denial specified in subsection (d) is a basis on which the agency must deny an application; if none of these grounds applies, the application must be approved.

The sentence following the seven grounds for denial, however, complicates matters. It states that if the FDA "finds that *clauses (1) through (6)* do not apply, [the agency] shall issue an order approving the application." *Id.* § 355(d) (emphasis added). Read in isolation, this sentence would suggest that subsection (d)(7)—the false or misleading labeling provision—does not furnish a sufficient basis,

standing alone, to deny an application. Yet this clause is in direct conflict with the language in Section 355(c) and (d) discussed above, which requires the agency to deny an application on any of the seven grounds, including false or misleading labeling. The statute does not explain this internal inconsistency, and there is no other language in Section 355 suggesting that subsection (d)(7) should be treated differently from the other six grounds for denial.

PMRS contends that the reference to "clauses (1) through (6)" in Section 355(d) means the FDA cannot refuse to approve an NDA based solely on a false or misleading label. Here, the agency relied exclusively on subsection (d)(7) in denying PMRS's application. PMRS argues that the Denial Order therefore contravened the plain text of the FDCA and was contrary to law within the meaning of the APA. *See* 5 U.S.C. § 706(2)(A).

The FDA responds that this inconsistency in the text reflects a scrivener's error resulting from a 1984 amendment to the FDCA that added a seventh ground for denying a new drug application. In the pre-1984 version of the statute, the false or misleading label provision appeared at subsection (d)(6) and was followed by the same reference to "clauses (1) through (6)" that appears in the current version. In other words, under the prior iteration of Section 355(d), a false or misleading label was a sufficient ground for denying an application. Congress amended the statute by inserting a new ground for denial at subsection (d)(6) and moving the false or misleading labeling clause to (d)(7)—but it left unchanged the reference to "clauses (1) through (6)" in the sentence that follows. *Compare* 21 U.S.C. § 355(d) (1982), *with* 21 U.S.C. § 355(d) (1988). The FDA maintains that nothing in the current statute indicates that Congress intended this renumbering to alter the longstanding statutory scheme by

permitting the FDA, for the first time, to approve an application that proposes false or misleading labeling. Indeed, the remainder of Section 355 directly contradicts that interpretation. Thus, the FDA maintains the only plausible reading is that Congress simply neglected to update one clause of Section 355(d) to include the renumbered ground (7).

We agree with the FDA that a false or misleading label is a sufficient ground for denial. As written, Section 355 states an irreconcilable contradiction—two provisions indicate that the agency can deny an application based only on false or misleading labeling, but another suggests it cannot. While we cannot "judicially amend[] a statute 'to provide for what [we] might think … is the preferred result,'" this case represents a rare situation where "there is no plausible reading of the plain text absent recognizing and correcting for the error." *United States v. Palmer*, 854 F.3d 39, 52–53 (D.C. Cir. 2017) (quoting *Lamie v. U.S. Tr.*, 540 U.S. 526, 542 (2004)). Under such circumstances, "it is not contrary to sound principles of interpretation … to give the totality of context precedence over a single word"—or, in this instance, a single number. Antonin Scalia, *Common-Law Courts in a Civil-Law System: The Role of United States Federal Courts in Interpreting the Constitution and Laws*, *in* A Matter of Interpretation: Federal Courts and the Law 3, 20–21 (Amy Gutmann ed., 1997).

Here, the totality of statutory context confirms that the FDA must deny an application if the label is false or misleading, consistent with the text in Section 355(c)(1)(A) and the beginning of Section 355(d). Section 355(e), for example, provides that the FDA may withdraw its prior approval of a new drug if "new information" reveals that the drug's label is "false or misleading in any particular." 21 U.S.C. § 355(e). It would be incoherent to allow the FDA to

withdraw approval of a drug for false or misleading labeling, but not to allow the FDA to deny approval on the same grounds. Similarly, neighboring sections of the FDCA that govern approvals of medical devices and animal drugs unambiguously direct the FDA to deny any application that proposes false or misleading labeling. *See id.* § 360e(d)(2)(D); *id.* § 360b(d)(1)(H). The language and structure of these provisions is substantially identical to Section 355(d), aside from Section 355(d)'s contradictory reference to "clauses (1) through (6)."[3] Thus, throughout the statute, Congress consistently prohibited the FDA from allowing drugs, medical devices, and other regulated products to reach the market with false or misleading labels. This context bolsters our conclusion that the 1984 amendments did not establish a novel standard for new drug applications that disrupts the broader statutory scheme. *Cf. Garcia-Carias v. Holder*, 697 F.3d 257, 263 (5th Cir. 2012) ("[A] statutory provision cannot be read in isolation, but necessarily derives meaning from the context provided by the surrounding provisions, as well as the broader context of the statute as a whole." (citation and quotation marks omitted)).

For similar reasons, the statutory history of Section 355(d) reinforces our interpretation. Before 1984, Section 355 unequivocally required the FDA to deny a new drug application based on false or misleading labeling. *See* 21 U.S.C. § 355(d) (1982). The 1984 amendments inserted a new subsection (d)(6), addressing patent information, but did not

[3] A separate chapter of the FDCA, addressing regulation of tobacco products, also directs the FDA to deny an application to market a tobacco product if the agency finds, "based on a fair evaluation of all material facts, the proposed labeling is false or misleading in any particular." 21 U.S.C. § 387j(c)(2)(C).

change the false or misleading labeling provision aside from moving it to subsection (d)(7). *See* 21 U.S.C. § 355(d) (1988). Construing the reference to "clauses (1) through (6)" to effectively read "clauses (1) through (7)" does the "least violence to the text." *Green v. Bock Laundry Mach. Co.*, 490 U.S. 504, 529 (1989) (Scalia, J., concurring in the judgment); *see also Lacson v. U.S. Dep't of Homeland Sec.*, 726 F.3d 170, 173 n.2 (D.C. Cir. 2013) ("Because there is no indication that Congress intended this technical change to affect the scope of [the statutory provision], we agree with both parties that the failure to replace the words 'subsection … (s)' with 'subsection … (r)' was a scrivener's error.").

PMRS asserts that we could "harmonize" the conflicting statutory provisions by reading them to require the FDA to approve an application that includes false or misleading proposed labeling "subject to revision of the label." Reply Br. 23. This interpretation, however, has absolutely no basis in the text and would require us to "rewrit[e] the statute rather than correct[] a technical mistake." *United States v. X-Citement Video, Inc.*, 513 U.S. 64, 82 (1994) (Scalia, J., dissenting).

True scrivener's errors are unusual and we should not lightly assume that Congress has made one. Here, however, reading the text of Section 355 in light of the broader context and structure of the statute demonstrates that the lingering reference to "clauses (1) through (6)" is best understood as an error. We will not privilege one contradictory numbered reference over the rest of the statutory text, context, and structure. Accordingly, we conclude the FDA did not act contrary to law in denying PMRS's NDA based solely on its finding that the proposed labeling was false or misleading.

B.

We next consider PMRS's claim that the FDA's decision to deny approval of PMRS's NDA was "arbitrary, capricious, … or otherwise not in accordance with law." 5 U.S.C. § 706(2)(A). As with all such claims, our review focuses on whether the agency's decision was "reasonable and reasonably explained," and "based on 'consideration of the relevant factors.'" *Nat'l Tel. Co-op. Ass'n. v. FCC*, 563 F.3d 536, 540 (D.C. Cir. 2009) (quoting *Motor Vehicle Mfrs. Ass'n, Inc. v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 43 (1983)). In the context of a challenge to the FDA's decisionmaking, we "give[] a high level of deference" to the agency's scientific analysis of the evidence before it, *Rempfer v. Sharfstein*, 583 F.3d 860, 867 (D.C. Cir. 2009) (quotation marks omitted), and must avoid "unduly second-guess[ing] [those] scientific judgments," *Cytori Therapeutics, Inc. v. FDA*, 715 F.3d 922, 923 (D.C. Cir. 2013). Applying these standards to the present case, we conclude the FDA acted reasonably and in accordance with applicable law in finding that PMRS's proposed label was false and misleading and in denying the NDA on that basis.

The FDA examined the evidence presented by PMRS and reasonably concluded that it did not support the specific statements included in PMRS's proposed labeling. PMRS's draft label and proposed product name represented that its drug possessed physical and chemical abuse deterrent properties. Yet the FDA found that PMRS failed to present substantial and reliable evidence showing that its "formulation … actually possess[es] those properties." 83 Fed. Reg. at 54,603. The reasons for this finding were explained in detail in the Denial Order, as well as in the FDA's earlier responses to PMRS. As an initial matter, the FDA emphasized that PMRS provided no evidence indicating

that the inclusion of a dye that would make an injectable solution derived from the drug "dark, opaque, [and] 'contaminated-looking'" would actually deter abuse. *Id.* at 54,598. The agency found this hypothesis particularly problematic given that people who abuse opioids "routinely take extraordinary risks in connection with their opioid abuse." *Id.* at 54,601. While PMRS criticizes the FDA for "focus[ing] myopically on the dye in denying the application," Reply Br. 4, PMRS does not point to any other scientific support for the label's statements about the drug's "inactive ingredients" that the FDA overlooked.

Similarly, the FDA found no support for the draft label's statement that the drug had "increased resistance to physical and chemical extraction" as compared to a previously approved opioid, Roxicodone. In the Denial Order, the FDA noted that this labeling claim "appear[ed] to rest on a misunderstanding of how th[e] term ['extraction'] is used in the context of abuse-deterrent opioids," because PMRS's data in fact showed that oxycodone could be easily extracted from its product to create a solution suitable for injection. 83 Fed. Reg. at 54,598 n.1. On appeal, PMRS argues that the FDA erred in its "cursory dismissal of PMRS's evidence on 'solubility' and 'extraction,'" but never explains precisely what the FDA is supposed to have gotten wrong. PMRS Br. 31.

The FDA also noted that PMRS had failed to submit any evidence indicating that its drug would "deter abuse by snorting," 83 Fed. Reg. at 54,601, but acknowledged that PMRS had "conceded … that the formulation should not be considered to have this property," *id.* at 54,598 n.2. PMRS argues that the agency should not have "relie[d] heavily" on the absence of such evidence since PMRS had abandoned its original claim that the drug would deter nasal abuse. PMRS

Br. 30. While the FDA's discussion on this point admittedly is not a model of clarity, it does not undermine the validity of the agency's overall decisionmaking or its conclusion that PMRS provided no evidence that its formulation had abuse deterrent properties of any kind.

The FDA next considered the disclaimers PMRS included in its draft label—stating there was "no clinical evidence" that its product "has a reduced abuse liability compared to immediate-release oxycodone," and that abuse of its product is "still possible"—and concluded that they did not make the label accurate. 83 Fed. Reg. at 54,602 n.17. Juxtaposed with the label's other statements about abuse deterrence, the FDA found the disclaimers conveyed that PMRS's drug had abuse deterrent properties, even if it was not "abuse-proof." *Id.*[4]

Finally, the FDA articulated a rational explanation for its refusal to consider the revisions to the draft label that PMRS submitted after its hearing request. According to the Denial Order, by requesting a hearing, PMRS asked the FDA to determine whether its existing application could be approved, not to opine on whether PMRS could at some point formulate a different NDA that "might address some of the deficiencies" identified by the FDA. *Id.* at 54,600 n.9. We find this position to be consistent with the FDA's regulations, which require applicants to choose between resubmitting an application and

[4] In its reply brief, PMRS claims that the FDA "[did] not identify any of this text as affirmatively false or misleading," but does not engage with the FDA's actual analysis. Reply Br. 9. We will not consider such a cursory argument raised for the first time on reply. *Dodge of Naperville, Inc. v. NLRB*, 796 F.3d 31, 41 (D.C. Cir. 2015).

requesting a hearing. *See* 21 C.F.R. § 314.110(b).[5] In any event, the FDA explained that even the proposed revisions would not address the FDA's central concern "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," because PMRS still proposed to include "ADF" in the product name. 83 Fed. Reg. at 54,600 n.9.

PMRS contends that the FDA departed from its precedent by refusing to consider these proposed revisions. But it fails to identify any examples of the FDA approving an NDA on the basis of significant labeling revisions proposed after a hearing request, particularly where there was no evidence showing the formulation had any abuse deterrent properties. Indeed, in the only arguably analogous example PMRS points to, the FDA approved an opioid formulation with an amended label describing the drug's abuse deterrent properties only after finding that the applicant "provided sufficient data to demonstrate that the … formulation appears to provide an incremental decrease in" persistent nasal abuse. *See* FDA, Ctr. for Drug Eval. & Research, App. No. 202080Orig1s000, Summary Review, at 18 (June 17, 2011). The FDA found no comparable evidence here.

PMRS's remaining arguments all rest on the same premise: The FDA should have accepted PMRS's alternative,

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[5] The regulation provides that after receiving a complete response letter, an applicant "must take one of" three actions: (1) "Resubmit the application …, addressing all deficiencies identified in the complete response letter"; (2) "[w]ithdraw the application"; or (3) "[a]sk the agency to provide the applicant an opportunity for a hearing on the question of whether there are [statutory] grounds for denying approval of the application." 21 C.F.R. § 314.110(b).

superior approach to opioid abuse deterrence and approved the NDA notwithstanding the lack of evidence for the label's assertions about the drug's abuse deterrent formulation. Yet the simple fact is that even if the FDA were willing to consider PMRS's alternative evidence of abuse deterrence, such evidence would do nothing to fix the inaccuracies in the label PMRS proposed.

First, PMRS argues the FDA disregarded the statutory requirement to consider the accuracy of a drug's labeling in light of "all material facts," 21 U.S.C. § 355(d)(7), which, according to PMRS, includes the "conditions of use prescribed, recommended, or suggested in the proposed labeling," *id.* § 355(d)(5). Here, PMRS proposed labeling its drug with an indication for acute, rather than chronic, pain management, and following the Center for Disease Control's dosing recommendations for immediate-release opioids. According to PMRS, the FDA's refusal to consider those "conditions of use" in assessing the accuracy of the draft label rendered the Denial Order contrary to law.

Next, PMRS argues that the agency failed to consider an important aspect of the problem when it arbitrarily refused to "'even consider the possibility' that PMRS's indications and studies could support an abuse deterrent label." PMRS Br. 43 (emphasis omitted) (quoting *State Farm*, 463 U.S. at 48). PMRS maintains that the FDA's approach to abuse deterrence, as set out in the 2015 Guidance, is scientifically unsound, and that PMRS's purportedly novel focus on duration and dosing indications is more likely to deter abuse.

In effect, PMRS seeks to enlist the court in its preferred approach to abuse deterrence. Whatever the validity of its broader claims, PMRS's proposal to label its product for acute pain management and to recommend lower daily dosing—

features that have nothing do with a drug's physical or chemical properties—has no bearing on the accuracy of its labeling claims about the product's abuse deterrent formulation. While PMRS contends on appeal that its proposed label "described the *product*, not just its 'formulation,'" Reply Br. 4, the words of the proposed label belie that contention. PMRS sought to designate its drug as an "abuse deterrent *formulation*," not an abuse deterrent *product.*

The bottom line, as the FDA pointed out, is that PMRS provided "no evidence establish[ing] … that this formulation has the abuse-deterrent properties PMRS propose[d] to include in its product labeling." 83 Fed. Reg. at 54,601.[6] Because both the product name and the draft label focused on

[6] For this reason, PMRS's separate claim that the FDA improperly treated the 2015 Guidance as binding law also fails. It is well established that "[o]nly 'legislative rules'" promulgated through public notice and comment "have the force and effect of law." *Appalachian Power Co. v. EPA*, 208 F.3d 1015, 1020 (D.C. Cir. 2000). PMRS contends that the FDA treats the 2015 Guidance as *requiring* applicants seeking labeling for abuse deterrence to present evidence from Category 1, 2, and 3 studies, without having put those evidentiary guidelines through notice and comment rulemaking. The problem for PMRS is that the FDA did not premise its denial solely on the absence of Category 1, 2, and 3 studies—it denied the NDA due to the absence of any evidence supporting PMRS's labeling claims. The FDCA requires applicants to support a proposed label with "substantial evidence." 21 U.S.C. § 355(d). Because PMRS failed to provide substantial evidence of any kind—Guidance-compliant or otherwise—it could not have met the statutory standard. On these facts, we see no basis to conclude that the FDA applied the 2015 Guidance "as if it were binding." *Nat'l Mining Ass'n v. McCarthy*, 758 F.3d 243, 253 (D.C. Cir. 2014).

unproven abuse deterrent physical and chemical properties of PMRS's drug, they were false and misleading regardless of whether PMRS is correct that there are other, more effective ways of reducing opioid abuse. In other words, there was no reason for the FDA to separately consider the particular "conditions prescribed, recommended, or suggested in [PMRS's] proposed labeling" once it had found that the label would be false and misleading regardless of those conditions. *See* 21 U.S.C. 355(d).

The FDCA requires the FDA to determine whether a proposed label is false or misleading "based on a fair evaluation of all *material* facts." *Id.* § 355(d)(7) (emphasis added). For the reasons already stated, PMRS's evidence regarding alternative approaches to abuse deterrence was immaterial to the agency's assessment of the specific claims in PMRS's proposed label. In the absence of countervailing evidence, we have no basis to question the agency's conclusion that the operative version of PMRS's proposed label created the false and misleading impression that the drug possessed abuse deterrent physical and chemical properties. *See Rempfer*, 583 F.3d at 867 (according heightened deference to FDA where "there [was] no scientific evidence in the administrative record to contradict [its] judgment"). Meaningful review of the agency's actions does not require us to step into the FDA's shoes and reassess its scientific judgments—a role that we are "ill-equipped" to play "under the guise of the APA's arbitrary and capricious standard." *Cytori Therapeutics*, 715 F.3d at 927. Here, the FDA examined the material factors, considered the record as a whole, and provided a reasonable explanation for its decision to deny PMRS's application. *Am. Wild Horse Pres. Campaign v. Perdue*, 873 F.3d 914, 923 (D.C. Cir. 2017). The APA requires no more.

III.

Lastly, we consider whether the FDA properly exercised its discretion in refusing to grant PMRS's request for a hearing on its application. *See* 21 U.S.C. § 355(c)(1) (after reviewing an NDA, the agency must either approve the application or "give the applicant notice of an opportunity for a hearing … on the question whether such application is approvable"); *accord* 21 C.F.R. § 314.200. Our review of an agency's decision to grant or deny a hearing is "necessarily deferential," and is "limited to an evaluation of whether [the agency] has given adequate consideration to all relevant evidence in the record." *Nat'l Corn Growers Ass'n v. EPA*, 613 F.3d 266, 271–72 (D.C. Cir. 2010) (citation and quotation marks omitted). To warrant a hearing, a party's submission must raise a genuine and substantial issue of fact "that might affect the outcome … under the governing law." *John D. Copanos & Sons, Inc. v. FDA*, 854 F.2d 510, 522–23 (D.C. Cir. 1988) (citation omitted); *see also* 21 C.F.R. §12.24(b)(4) ("A hearing will not be granted on factual issues that are not determinative with respect to the action requested."). For many of the reasons discussed in Part II.B, we find the FDA acted within its discretion in denying PMRS's hearing request.

As already explained, the FDA considered PMRS's application and reasonably determined that there was no evidence to support PMRS's claim that its product had an abuse deterrent "formulation." PMRS's evidence regarding duration and dosing therefore could not remedy the false and misleading nature of its draft label, which focused on the product's chemical and physical properties. This meant that PMRS's alternative evidence, even if considered, necessarily could not create a "genuine and substantial issue of fact" that, if resolved in PMRS's favor, would justify approval of

PMRS's application. 21 C.F.R. § 12.24(b). In other words, because PMRS's proffered evidence created no relevant factual dispute, it did not provide a basis on which to grant a hearing. *See Copanos*, 854 F.3d at 523.

Nor can we conclude that PMRS's eleventh hour attempt to modify its proposed label created a genuine issue of fact requiring a hearing. PMRS submitted a proposed revision to its draft label in August 2018—many months after receiving the complete response letter and electing to request a hearing rather than revise and resubmit its application. As already noted, we find the FDA's explanation for its refusal to consider revisions at this late stage to be reasonable. *See supra* at 16–17.

Finally, we do not believe the FDA exceeded its discretion in refusing to grant PMRS's request for a hearing on broader policy issues related to the problem of opioid abuse deterrence. PMRS might be dissatisfied with the agency's overall approach, but the FDA's regulations make clear that "a hearing will not be granted on issues of policy and law." *See* 21 C.F.R. § 12.24(b)(1). Particularly in light of our "necessarily deferential" review of agency hearing requests, *Nat'l Corn Growers Ass'n*, 613 F.3d at 271, we will not lightly overrule an agency's determination that a hearing is not "otherwise in the public interest." *See* 83 Fed. Reg. at 54,603 (citing 21 C.F.R. § 314.200(g)(6)). In the Denial Order, the FDA described the numerous fronts on which it is working to tackle the pervasive crisis of prescription opioid addiction and abuse. *Id.* The FDA chose to set such policies in publicly available guidance documents, thereby providing notice and predictability to regulated entities. We find no abuse of discretion in the FDA's determination that a hearing on one manufacturer's new drug application is not the

appropriate forum to address these important public health issues.

* * *

The FDA reasonably concluded that PMRS's proposed labeling was false and misleading under 21 U.S.C. § 355(d)(7). On that basis, it denied PMRS's request for a hearing and refused to approve its NDA. Because the FDA complied with applicable law, examined the evidence provided by PMRS, and explained its reasoning, we uphold the agency's action. The petition for review is denied.

So ordered.