United States Court of Appeals

FOR THE DISTRICT OF COLUMBIA CIRCUIT

No. 18-1112 **September Term, 2018**

FILED ON: OCTOBER 30, 2018

BRECKENRIDGE PHARMACEUTICAL, INC. AND NEXGEN PHARMA, INC,
PETITIONERS

v.

FOOD & DRUG ADMINISTRATION AND ALEX MICHAEL AZAR, II, IN HIS OFFICIAL CAPACITY AS SECRETARY OF THE UNITED STATES DEPARTMENT OF HEALTH AND HUMAN SERVICES,
RESPONDENTS

BAYER HEALTHCARE LLC,
INTERVENOR

Consolidated with 18-1120, 18-1130

On Petitions for Review of a Final Order of
the Food & Drug Administration

Before: GARLAND, *Chief Judge*, MILLETT, *Circuit Judge*, and WILLIAMS, *Senior Circuit Judge*.

J U D G M E N T

The court considered these appeals on the record from the Food and Drug Administration ("FDA"), and on the briefs and arguments of the parties. The court has given the issues full consideration and has determined that they do not warrant a published opinion. See D.C. CIR. R. 36(d). For the reasons stated below, it is

ORDERED and **ADJUDGED** that FDA's order and hearing denial are **AFFIRMED**.

The Federal Food, Drug, and Cosmetic Act ("FD&C Act") establishes two mutually exclusive categories of drugs—prescription and over-the-counter ("OTC"). A drug that meets

prescription criteria under 21 U.S.C. § 353(b)(1) is misbranded if it *fails* to display an "Rx only" symbol, § 353(b)(4)(A), while a drug that does not meet those criteria is misbranded if it *displays* an "Rx only" symbol, § 353(b)(4)(B). We consider here whether petitioners' prescription version of the laxative MiraLax (polyethylene glycol 3350 or "PEG3350") is misbranded under (b)(4)(B) because it is the same "drug" as one that the FDA has determined can safely be sold over the counter and thus no longer meets (b)(1)'s prescription requirements.

In 1999, FDA approved a New Drug Application ("NDA") for prescription MiraLax from Braintree Laboratories, Inc. Piggybacking off this approval, petitioners filed Abbreviated New Drug Applications ("ANDAs") for generic versions of prescription MiraLax; the FDA approved the applications in 2004-06. FDA approved Braintree's new NDA for OTC MiraLax by a letter dated October 6, 2006. Joint Appendix ("J.A.") 732-34. As FDA later explained in its "Notice for an Opportunity for Hearing on a Proposal to Withdraw Approval of Prescription [PEG3350 ANDAs]" ("NOOH"), its approval of the NDA for an OTC version meant that PEG3350 no longer met the criteria for a prescription drug under (b)(1)(B) unless there was a "meaningful difference" between the prescription and OTC versions of the drug. 73 Fed. Reg. at 63,491, 63,492/3 (Oct. 24, 2008). FDA determines the existence of a "meaningful difference" by looking to "such factors as the indication, strength, route of administration, dosage form, or patient population," *id*. at 63,492/3, and in the NOOH it found no such differences, *id*. at 63,492-94.

After receiving objections and submissions from petitioners, and an unexplained six-year delay, FDA in May 2014 issued a notice and attached a proposed order denying petitioners' requests for a hearing and withdrawing petitioners' ANDAs, J.A. 300-59. It made the proposed order final in its 2018 Order now under review. See 83 Fed. Reg. at 13,994 (Apr. 2, 2018).

Petitioners challenge FDA's determination of no "meaningful difference" and raise process-based challenges alleging lack of adequate notice and improper denial of a hearing. Finding these claims wanting, we affirm FDA's withdrawal of petitioners' ANDAs.

* * *

In the NOOH, FDA found that on each of the factors pertinent to a "meaningful difference," OTC and prescription MiraLax were identical (or nearly so). They have the same (1) active ingredient (PEG 3350), (2) indication (occasional constipation), (3) strength (17 grams), (4) route of administration (oral), and (5) dosage form (powder), and (6) patient population (patients 17 years of age or older). See 83 Fed. Reg. at 13,997/1; 73 Fed. Reg. at 63,492/3. (FDA appears to define "pediatric population" as, among other things, "from birth to 16 years," in the context of prescription drug labeling, 21 C.F.R. § 201.57(c)(9)(iv)(A), so that 17-year-olds are "adults." In that case, there is no difference as to patient population with the OTC version. In any event, petitioners do not argue that differences in MiraLax use between 17- and 18-year-olds are meaningful.) None of this is in dispute, not least because petitioners had to make those showings in their ANDA applications (with patient population addressed in the labeling). See Pet. Br. 7. Factors (1)-(6) are identical (or nearly so) between the two drugs being compared to assess "meaningful difference": Braintree's 1999 prescription NDA (the reference drug for petitioners' ANDAs) and Braintree's 2006 OTC NDA. Compare J.A. 728-29 and 730-31 with

736.

So where do petitioners see a "meaningful difference"? They point us to duration of use, compared below:

TABLE 3—LABELING REGARDING DURATION OF USE FOR PRESCRIPTION AND NONPRESCRIPTION PEG 3350

	Prescription MiraLAX	Nonprescription MiraLAX
Duration of Use	This product should be used for 2 weeks or less or as directed by a physician.	Use no more than 7 days. Stop use and ask a doctor if you need to use a laxative for longer than 1 week.

83 Fed. Reg. at 14,007.

We find no error in FDA's determination that the difference here was not "meaningful." We note that the agency left open the possibility that differences in duration of use—in other circumstances—could add up to a "meaningful difference. " See 83 Fed. Reg. at 13,999/3 ("[T]he Commissioner *in this proceeding* declines to conclude that duration of use alone, without an additional more fundamental difference between the products, is sufficient to establish a meaningful difference.") (emphasis added); see also *id.* at 13,999/1 (recognizing that "duration of therapy" may indicate a "meaningful" difference between prescription and over-the-counter drugs); 73 Fed. Reg. at 63,493/1 (same). We necessarily leave the issue open as we have before us no blanket rule that variations in use duration cannot qualify as "meaningful."

A week-by-week look best pinpoints the difference in duration of use between the two MiraLax versions. We start with week two. There, both versions are the same—any use in the second week requires physician oversight for prescription and OTC alike. Under the prescription version, the patient could only have secured the drug by consulting a physician. Under the OTC version, patients are instructed to "[u]se no more than 7 days. Stop use and ask a doctor . . . ." 83 Fed. Reg. at 14,007.

What about week one? There, at least, petitioners identify one potential difference: whereas in the prescription version physician approval is required, in the OTC context it is not. (That the prescription label recommends a *two-week* initial period of use, whereas the OTC label recommends a *one-week* initial period, has no independent weight, since physician approval is still required after the first week in both cases.) Does that contrast during week one amount to a "meaningful difference" between the two versions of MiraLax—keeping in mind the *identical* active ingredients, indications, strengths, routes of administration, dosage forms, and nearly identical patient populations? FDA's answer says it does not.

Petitioners' dominant objection centers on safety concerns rooted in lay misdiagnosis or "masking"—through use of the OTC product—of more serious conditions like cancer, stricture, or opioid abuse. See, e.g., Pet. Br. 15. But the OTC label already addresses these concerns, so that any safety difference between the OTC and prescription products effectively vanish. FDA has found—and petitioners do not dispute—that MiraLax is generally effective for its sole indication (occasional constipation) in "less [sic] than 7 days." 83 Fed. Reg. at 13,999/2. It is expected to produce bowel movements in 1-4 days. *Id*. That means the minority of MiraLax users for whom (1) symptoms do not subside within 1-4 days and (2) who have a masked

condition, will be under a physician's care on no later than the eighth day (assuming on-label use). In addition, some OTC users may take MiraLax only after consulting a physician, obviating masking concerns for this cohort. See *id.* at 14,009/3 ("[A] physician is free to instruct a patient on how and whether to use a nonprescription product."). Further, petitioners do not contest FDA's determination that OTC MiraLax is safe in this first week of use. See Oral Argument at 6:53 (Court: "So [FDA's] determination there that there was no safety need to maintain that drug with a prescription—you're not challenging that, right?" Counsel for Petitioners: "That's correct. . . . There's not a safety concern, assuming people that are using it for a week, which generally you hope they are. . . ."). In other words, the only difference appears to be the prescription drug's requirement of physician intervention during the first week—which FDA's approval of OTC MiraLax had found to be unnecessary from a safety perspective.

Petitioners seek to move outside this analysis by urging us to consider off-label use—that is, use of the OTC product for more than a week—in assessing FDA's reasoning. Pet. Br. 34. As petitioners see it, the market needs a prescription version of MiraLax with doctors acting as gatekeepers. They cite increased hospitalizations and deaths "attributed to the drug" after OTC approval. But the risk of off-label use applies to all or most drugs—prescription or OTC—and, presumably, an important feature of the drug classification system is that patients generally respond to labels. FDA, moreover, has "found that the product is safe and effective for use for self-medication as directed in the proposed nonprescription labeling." 83 Fed. Reg. at 14,009/3. The agency made this finding as part of its approval of OTC MiraLax, see 21 C.F.R. § 310.200(b) (referring to "use in self-medication as directed in proposed labeling")—an approval that petitioners do not contest, see Oral Argument at 6:43 (Court: "You're not challenging the previous decision to go from Rx to OTC on MiraLax are you?" Counsel for Petitioners: "Not at all."). We therefore find that FDA properly carried out its analysis within the context of on-label use. See 83 Fed. Reg. at 14,008/1-2. Finally, studies in connection with approval of OTC MiraLax found that it "would still be considered safe if a consumer chose to use it repeatedly before seeking advice from a physician." *Id*. at 14,008/2; see *id.* at 13,996/3. In sum, FDA reasonably concluded that petitioners' safety-based arguments provide no basis for a "meaningful difference" finding.

As to petitioners' argument that increased efficacy with longer use of MiraLax amounts to a separate basis for a "meaningful difference," two responses are warranted. See, e.g., Pet. Br. 12, 17, 31. First, since the indication for prescription and OTC MiraLax is *occasional* constipation, FDA explains that studies concerning longer-term efficacy are relevant primarily to confirm the *safety* of OTC MiraLax (not efficacy) for the sole indication at issue here. 83 Fed. Reg. at 14,008/1-2. Second, FDA observes that longer-term benefits would accrue under both versions, since a physician can recommend and approve longer-term use to OTC consumers past the first week. *Id.* at 14,007-08.

Finally, petitioners' comparisons with butenafine, terbinafine, and ibuprofen misfire. As to butenafine and terbinafine, it is true that FDA invoked risks of lay misdiagnosis in distinguishing OTC and prescription versions of those drugs (and allowing both). But the two versions in that instance were approved for different indications that call for "different levels of expertise to diagnose and treat." 83 Fed. Reg. at 14,012/1-2. And the risks involved

misidentifying a condition (tinea versicolor) that fell only under one indication—for which FDA required a prescription. Not so for MiraLax, which has only one indication for both versions. As for ibuprofen, the prescription and nonprescription versions of the drug "differ in the[ir] indications, dosage, and durations of use depending upon the indication." *Id*. at 14,015/1. Petitioners acknowledge as much, Pet. Br. 48, but insist that FDA never explains why a greater *number* of differences perforce adds up to a more "meaningful" or "fundamental" difference, *id*. We see no merit in this objection. Not only do both versions of ibuprofen (suspension and tablet) differ as to *three* relevant factors (indication, dose, duration of use), but differences within the first two factors reasonably support FDA's conclusion. In particular, both prescription versions permit treating primary dysmenorrhea, as well as signs and symptoms of rheumatoid arthritis and osteoarthritis, whereas the OTC versions do not. 83 Fed. Reg. at 14,014/2-3. And whereas the daily dosage limit for OTC ibuprofen tablets is set at 1,200 mg, the prescription version more than doubles that ceiling to 3,200 mg for certain indications. *Id*. at 14,014-15. No contrasts of this magnitude exist in the case of MiraLax. Thus the distinctions FDA draws between butenafine, terbinafine, and ibuprofen and MiraLax are plausible and do not advance petitioners' case. See *id*. at 14,010-12.

We thus conclude that FDA's determination that prescription MiraLax is misbranded for lack of a "meaningful difference" with OTC MiraLax is neither arbitrary nor capricious.

* * *

We also reject petitioners' process-based challenges to FDA's denial of a hearing on withdrawal of prescription MiraLax.

First, petitioners argue FDA had to articulate its "meaningful difference" standard by rulemaking under 21 U.S.C. § 353(b)(3). See Pet. Br. 24. But this misunderstands the source of FDA's authority here. To withdraw petitioners' ANDAs, FDA relied not on § 353(b)(3), but on its authority under 21 U.S.C. § 355(e)(3) – the second (3) in that oddly drafted subsection. See 73 Fed. Reg. at 63,492/2; 83 Fed. Reg. at 13,995/3, 14,016/2; FDA Br. 37. Petitioners do not challenge the correctness of FDA's reliance on that section.

Second, petitioners argue they did not receive proper notice of FDA's "meaningful difference" standard. We disagree. Despite minor variances in FDA's formulation of that standard in the 2008 NOOH and 2018 Order, petitioners faced no "significant ambiguity regarding the type of information that would warrant a hearing." *John D. Copanos & Sons, Inc. v. FDA*, 854 F.2d 510, 520 (D.C. Cir. 1988). As did the NOOH in *Copanos*, the NOOH here "discussed in detail the facts and evidence that formed the basis for the agency's proposed withdrawal of approval." *Id*. FDA set out the factors it deemed relevant and explained at length why it considered duration of use differences in the case of MiraLax "nonmeaningful." See 73 Fed. Reg. at 63,493-94. Thus, just as petitioner in *Copanos* could not "identify any evidence, or type of evidence, that it might have presented but for lack of notice as to its relevance," 854 F.2d at 520, petitioners fail to do so here. The NOOH gave "adequate notice of the type of information" petitioners would have had to adduce to merit a hearing. *Id*. The notice objection fails.

Third, petitioners contest FDA's refusal to engage substantively with their September 2014 submissions. See, e.g., J.A. 394-474. We find no (reversible) fault with FDA on this score. It properly declined to address those submissions under 21 C.F.R. § 314.200(g)(3) alone. Petitioners' frustration is understandable. FDA's (long-awaited) 2014 notice of a proposed order denying petitioners' request for a hearing cited § 314.200(g)(3), stating that petitioners "have 60 days after the receipt of this proposed order to respond with sufficient data, information, and analyses to demonstrate that there is a genuine and substantial issue of fact which justifies a hearing." See, e.g., J.A. 302, 305. The submissions were made within the time period prescribed by § 314.200(g)(3), taking into account time extensions granted by FDA. Now FDA argues that § 314.200(g)(3) must be "construed in harmony" with the more restrictive 21 C.F.R. § 314.200(c)(2), and that petitioners' September 2014 submissions are time-barred under (c)(2). FDA Br. 42. We do not address this issue, however, because we find FDA reasonably found the submissions insufficient to call for a hearing under (g)(3) alone. FDA explained that those submissions are "not relevant," because they are "not related to the factors set forth in the ANPRM and the NOOH as material to determining meaningful difference." 83 Fed. Reg. at 14,001/2. For example, (1) findings about MiraLax use for chronic constipation; (2) physician surveys about which MiraLax version they associate with shorter and longer use; (3) data on adverse effects after OTC approval; (4) prescription MiraLax sales data; and (5) existence of federal funding to study PEG 3350 use in pediatric populations, do not bear on comparisons of the active ingredient, indication, strength, route of administration, dosage form, or patient population. Accordingly, those submissions cannot raise "a genuine and substantial issue of fact which justifies a hearing." 21 C.F.R. § 314.200(g)(3).

In sum, the "meaningful difference" standard did not need to be set out via rulemaking, petitioners had adequate notice of that standard, and FDA did not reason arbitrarily or capriciously in declining to give weight to petitioners' September 2014 submissions under (g)(3).

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Pursuant to D.C. CIR. R. 36(d), this disposition will not be published. The Clerk is directed to withhold issuance of the mandate until seven days after resolution of any timely petition for rehearing or rehearing en banc. See FED. R. APP. P. 41(b); D.C. CIR. R. 41(b).

FOR THE COURT:
Mark J. Langer, Clerk

BY: /s/
Ken Meadows
Deputy Clerk