United States Court of Appeals

FOR THE DISTRICT OF COLUMBIA CIRCUIT

Submitted March 2, 2022 Decided June 3, 2022

No. 20-1525

NOSTRUM PHARMACEUTICALS, LLC,
PETITIONER

v.

UNITED STATES FOOD AND DRUG ADMINISTRATION,
RESPONDENT

On Petition for Review of Orders
of the Food and Drug Administration

Shashank Upadhye was on the briefs for petitioner. *Douglas B. Farquhar* entered an appearance.

Brian M. Boynton, Acting Assistant Attorney General at the time the brief was filed, U.S. Department of Justice, *Scott McIntosh* and *Joshua Dos Santos*, Attorneys, *Daniel J. Barry*, Acting General Counsel, U.S. Department of Health and Human Services, *Wendy Vicente*, Acting Deputy Chief Counsel for Litigation, and *Leslie Cohen*, Associate Chief Counsel, were on the brief for respondent.

Before: TATEL[*] and MILLETT, *Circuit Judges*, and EDWARDS, *Senior Circuit Judge*. [†]

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

MILLETT, *Circuit Judge*: Nostrum Pharmaceuticals, LLC is a drug manufacturer seeking to market various strengths and formulations of generic theophylline, a drug used to treat asthma and other respiratory conditions. To that end, Nostrum submitted a supplemental abbreviated new drug application to the Food and Drug Administration ("FDA"). This application remains pending. As part of the FDA's review process, an agency division sent Nostrum a so-called "complete response letter" that flagged deficiencies in the application and explained how Nostrum could remedy them. Nostrum sought reconsideration of only a portion of the complete response letter, which the division denied. Nostrum now petitions for review of the complete response letter and the denial of reconsideration. Because neither agency action constitutes a final rejection of the application, we lack jurisdiction to hear Nostrum's petition and therefore dismiss it.

I

A

Under the Food, Drug, and Cosmetic Act, a drug manufacturer seeking to market a generic drug must submit an abbreviated new drug application to the FDA showing that the

[*] Judge Tatel assumed senior status after this case was argued and before the date of this opinion.

[†] This petition was considered on the record from the Food and Drug Administration and on the briefs filed by the parties. *See* FED. R. APP. P. 34(a)(2); D.C. CIR. R. 34(j).

new drug is "bioequivalent" to a drug that has already been approved, which is known as the "listed drug." 21 U.S.C. § 355(j)(2)(A)(iv). The FDA considers two drugs bioequivalent if there is no "significant difference in the rate and extent to which" their active ingredients become "available at the site of drug action[,]" typically in the blood. 21 C.F.R. § 314.3. The FDA's regulations include guidelines on how to conduct bioequivalence studies. *See, e.g.*, 21 C.F.R. §§ 320.26, 320.29. Additionally, if a manufacturer wishes to make a "major manufacturing change" to the production of its already approved generic drug, it must submit a supplemental application to the FDA. 21 U.S.C. § 356a(c)(1); 21 C.F.R. §§ 314.70(b)(1), 314.97.

Once a drug manufacturer submits an application to the FDA, a multi-step review process begins. The FDA may refuse to approve an application for a number of reasons, including a lack of data sufficient to show that the proposed generic drug is bioequivalent to the reference drug. 21 C.F.R. § 314.127(a)(6)(i). If, in the course of reviewing an application, the FDA or one of its divisions concludes that an application has a defect that could potentially cause the agency to reject the application, it issues a "complete response letter[.]" *Id.* § 314.110(a).

A complete response letter "will describe all of the specific deficiencies" that the agency identified in the application and, "[w]hen possible," will "recommend actions that the applicant might take to place the application * * * in condition for approval." 21 C.F.R. § 314.110(a)(1), (4). If the applicant's responses would "require extensive assessment[,]" the agency categorizes them as "major" amendments. CENTER FOR DRUG EVALUATION & RESEARCH, U.S. FOOD & DRUG ADMIN., ANDA SUBMISSIONS—AMENDMENTS TO ABBREVIATED NEW DRUG APPLICATIONS UNDER GDUFA: GUIDANCE FOR

INDUSTRY 4 (July 2018) [hereinafter AMENDMENTS TO ABBREVIATED NEW DRUG APPLICATIONS].

An applicant who receives a complete response letter has several options for proceeding. First, it may "[r]esubmit the application * * *, addressing all deficiencies identified in the complete response letter." 21 C.F.R. § 314.110(b)(1). Second, it may "[w]ithdraw the application * * * without prejudice to a subsequent submission." *Id.* § 314.110(b)(2). Third, it may decline to revise its application and request a hearing "on the question of whether there are grounds for denying approval of the application[.]" *Id.* § 314.110(b)(3). Additionally, FDA draft guidance permits applicants to seek reconsideration of a complete response letter by the division that issued the letter. *See* CENTER FOR DRUG EVALUATION & RESEARCH, U.S. FOOD & DRUG ADMIN., REQUESTS FOR RECONSIDERATION AT THE DIVISION LEVEL UNDER GDUFA: GUIDANCE FOR INDUSTRY 3–6 (Oct. 2017) [hereinafter "RECONSIDERATION GUIDANCE FOR INDUSTRY"]. If the applicant does nothing for a full year after the complete response letter is issued, the FDA may, after some additional steps, deem the application withdrawn without prejudice to resubmission. 21 C.F.R. § 314.110(c).

If an applicant does not want to make the proposed changes, it may choose the third option and ask for a hearing. At that point, the FDA may go ahead and approve the application as is. 21 C.F.R. § 314.110(b)(3). Or it could propose to "refuse to approve the application * * * and give the applicant written notice of an opportunity for a hearing * * * on the question of whether there are grounds for denying approval of the application[.]" *Id.*; *see id.* § 314.200(a) (describing this stage of the agency decisionmaking process as a "*proposal* to refuse to approve an application") (emphasis added). The FDA regulations governing such hearings allow for the submission of evidence and arguments. *Id.*

§ 314.200(c)–(e). The Commissioner of Food and Drugs may then either enter summary judgment, *id.* § 314.200(g)(1)–(4), or hold a hearing "if there exists a genuine and substantial issue of fact or if [he] concludes that a hearing would otherwise be in the public interest[,]" *id.* § 314.200(g)(6). If, after all this, the Commissioner issues an "order * * * refusing * * * approval of an application[,]" that order is subject to judicial review. 21 U.S.C. § 355(h); *see also id.* § 355(j)(5)(E).

B

Nostrum manufactures generic theophylline extended-release tablets. Theophylline is used to treat a number of chronic lung diseases such as asthma, emphysema, and bronchitis. When theophylline is administered at the appropriate blood concentration, it can be effective. The challenge is that, for theophylline, "[t]here is little separation between effective concentrations and concentrations associated with serious toxicity[,]" and "[s]ub-optimal concentrations lead to severe therapeutic failure." OFFICE OF GENERIC DRUGS, U.S. FOOD & DRUG ADMIN., ASSESSMENT OF THEOPHYLLINE AS A NARROW THERAPEUTIC INDEX DRUG 1 (Jan. 12, 2017). In other words, small variations in theophylline's dosage can have serious adverse health consequences for patients. For that reason, the FDA has classified theophylline as a "narrow therapeutic index" drug.

Bioequivalence is commonly shown through a "two-way study" in which subjects are administered one dose each of the test drug and the listed drug, and the rate and extent of absorption of the two drugs is compared. But in light of the unique safety concerns that narrow therapeutic index drugs pose, the FDA advises that drug manufacturers submit more rigorous bioequivalence studies for generic narrow therapeutic index drugs than for other generics. Specifically, the FDA's

preferred method of demonstrating a narrow therapeutic index drug's bioequivalence is a "fully replicated crossover design" study. *See, e.g.*, CENTER FOR DRUG EVALUATION & RESEARCH, U.S. FOOD & DRUG ADMIN., SUMMARY MINUTES OF THE ADVISORY COMMITTEE FOR PHARMACEUTICAL SCIENCE AND CLINICAL PHARMACOLOGY 5 (July 26, 2011). A fully replicated crossover design study requires that subjects be given two doses each of the test and the listed drug so that researchers can measure the difference in rate and extent of absorption as between two doses of the same drug administered at different times to the same subject. Basically, this study design is meant to confirm that the generic drug is as reliable as the listed drug in being absorbed by the same person in a consistent manner across multiple doses.

C

In 2020, Nostrum submitted a supplemental abbreviated new drug application seeking, among other things, approval to market a 450 milligram strength of its theophylline extended-release tablets and to reformulate its previously approved 100, 200, and 300 milligram strengths. Nostrum sought to demonstrate the 450 milligram strength's bioequivalence by submitting two-way studies. Nostrum also asked for a waiver of the requirement to show bioequivalence for its reformulated strength tablets.

On July 21, 2020, a division within the Office of Generic Drugs issued a complete response letter notifying Nostrum that its supplemental abbreviated new drug application could not be approved "in its present form." Joint Appendix ("J.A.") 611. The letter advised that "[t]he Agency has recently determined that theophylline is a narrow therapeutic index * * * drug[,]" and so Nostrum's two-way studies "were insufficient to demonstrate" bioequivalence. J.A. 612. The division asked

Nostrum to conduct bioequivalence studies "using a fully replicated crossover design[,]" which it identified as "the most accurate, sensitive, and reproducible approach" to bioequivalence testing. J.A. 612 (citing 21 C.F.R. § 320.24(a)). It also denied Nostrum's request for a waiver of bioequivalence studies for its lower-strength formulations. The letter identified other issues for Nostrum to address, such as dissolution testing and labeling.

The division categorized the gaps in Nostrum's application as "major[,]" and it advised Nostrum that it could respond by taking one of the actions available under 21 C.F.R. § 314.110(b)—namely, make the requested changes, withdraw its application, or request a hearing before the Commissioner. J.A. 615.

Nostrum twice requested reconsideration from the division. In August 2020, it asked the division to reclassify the defects in its application as "minor" rather than "major" so that it could avoid the case-processing consequences of a major classification. *See* J.A. 619 (Nostrum's reconsideration request); AMENDMENTS TO ABBREVIATED NEW DRUG APPLICATIONS 3–5 (discussing the distinctions between major and minor amendments). A month later, the division denied that request. In September 2020, Nostrum requested that the division reconsider several of the other issues raised by the complete response letter. The status of that request is under seal.

D

On December 30, 2020, with its second reconsideration request still pending, Nostrum petitioned this court for review of the complete response letter and the denial of its first request for reconsideration, arguing that the FDA acted arbitrarily and

capriciously in requiring Nostrum to demonstrate bioequivalence using a fully replicated study.

The FDA moved to dismiss the petition on the ground that neither the complete response letter nor the reconsideration denial were reviewable final agency actions.

In March 2021, while that motion to dismiss was pending, Nostrum sent the FDA a "major" "resubmission" of its supplemental abbreviated new drug application, with the stated goal of maintaining the pendency of its application before the agency. Nostrum Mot. to Govern Further Proceedings 5–6 ("Nostrum submitted the * * * Letter to FDA in an effort to stave off an automatic withdrawal[.]"). In the main, Nostrum vigorously disputed the complete response letter's bioequivalence conclusions and the need to conduct new studies. *Id.* At the same time, the resubmitted application did "respond[] to all the other issues detailed in the Complete Response Letter" in the hope that providing "satisfactory answers to FDA's other concerns" would "protect" its application. *Id.* at 9–10.[1]

II

As relevant here, we have jurisdiction to review only "an order of the Secretary refusing * * * an application under this section." 21 U.S.C. § 355(h). Consequently, our review is limited to final rejections of drug applications, not interim decisions or nonbinding statements subject to further review or change. *See Pharmaceutical Mfg. Rsch. Servs., Inc. v. FDA*,

[1] The court's motion panel referred to this panel the FDA's motion to dismiss the petition, and a separate motion filed by Nostrum to supplement the administrative record with certain communications sent by Nostrum staff to FDA officials and materials relating to past abbreviated new drug applications.

957 F.3d 254, 259 (D.C. Cir. 2020) (Section 355(h) "permits applicants to appeal an FDA order *denying approval* of a new drug application[.]") (emphasis added).

A

We hold that courts lack jurisdiction to review a complete response letter issued by an FDA division because it is not an "order of the Secretary" that "refus[es] * * * approval of an application[.]" 21 U.S.C. § 355(h). Rather, a complete response letter is an interim step in the FDA's consideration of an application. More must happen before the FDA's final determination on the application is made. *Cf. Bennett v. Spear*, 520 U.S. 154, 178 (1997) (decisions "of a merely tentative or interlocutory nature" are not final agency action).

The FDA's regulations are explicit that complete response letters simply afford applicants the opportunity to provide additional information before the agency makes a final decision on the application. *Cf. California Cmtys. Against Toxics v. EPA*, 934 F.3d 627, 631 (D.C. Cir. 2019) ("[W]hen assessing the nature of an agency action (including whether it is final), * * * courts should take as their NorthStar the unique constellation of statutes and regulations that govern the action at issue."). That is why a complete response letter "will describe all of the specific deficiencies that the agency has identified in an application[.]" 21 C.F.R. § 314.110(a)(1). It will also identify any shortcomings in the data an applicant has submitted. *Id.* § 314.110(a)(3). And the letter will, when possible, "recommend actions that the applicant might take to place the application or abbreviated application in condition for approval." *Id.* § 314.110(a)(4). In other words, a complete response letter "inform[s] sponsors of changes that must be made before an application can be approved, with no implication as to the ultimate approvability of the application."

Applications for Approval to Market a New Drug; Complete Response Letter; Amendments to Unapproved Applications, 73 Fed. Reg. 39,588, 39,589 (July 10, 2008).

So rather than end the agency process, a complete response letter opens multiple doors for further processing of an application. After receiving a letter, the applicant may choose to withdraw its application without prejudice, 21 C.F.R. § 314.110(b)(2), revise its application, *id.* § 314.110(b)(1), stand on its application by requesting an opportunity for a hearing, *id.* § 314.110(b)(3), or seek reconsideration at the division level, RECONSIDERATION GUIDANCE FOR INDUSTRY 3–6.

If an applicant requests an opportunity for a hearing, the FDA may decide to approve the application as is. 21 C.F.R. § 314.110(b)(3). If it does not, the applicant may make its case to senior FDA leadership. First, the Director of the Center for Drug Evaluation and Research "will prepare an analysis of the request and a proposed order ruling on the matter." *Id.* § 314.200(f). Then, the Commissioner of Food and Drugs will consider the matter. *Id.* § 314.200(f)–(g). If the Commissioner rejects an application, either on summary judgment or after a hearing, he will enter an "order * * * refusing * * * approval" that is appealable to a court of appeals under 21 U.S.C. § 355(h). *See also* 21 U.S.C. § 355(j)(5)(E); *Pharmaceutical Mfg.*, 957 F.3d at 259.

All of that is to say that complete response letters are only a preliminary step in the agency's scientific review process. The recipient of a complete response letter "still enjoys an opportunity to convince the agency to change its mind[,]" *MediNatura, Inc. v. FDA*, 998 F.3d 931, 939 (D.C. Cir. 2021) (citation omitted), by persuading senior FDA leadership. As a matter of agency process and decisionmaking, the issuance of

a complete response letter is multiple steps removed from the conclusive "order * * * refusing * * * approval of an application[,]" 21 U.S.C. § 355(h), that is a prerequisite to our jurisdiction.

The facts of this case underscore the unfinished nature of the agency process at the complete-response-letter stage. Since petitioning this court for review, Nostrum has continued to press for approval of its still-pending application before the agency. In March 2021, Nostrum sent the FDA a letter disputing the complete response letter's bioequivalence conclusions, while also "responding to all the other issues" that the division had raised. Mot. to Govern 5–6, 9–10. Nostrum sent this letter for the express purpose of "stav[ing] off" an end to agency proceedings. *Id.* at 5; *see* 21 C.F.R. § 314.110(c)(1) (inaction by an applicant for a year after the issuance of a complete response letter may be construed as a "request by the applicant to withdraw the application"). Those measures would make no sense if the FDA had already issued an order "refusing * * * approval of [the] application[.]" 21 U.S.C. § 355(h).

Nostrum argues that the continued pendency of its application is no obstacle to our review because it remains at loggerheads with the FDA on the central question of how it can demonstrate its products' bioequivalence. Mot. to Govern 4, 12. The short answer is that Congress has conditioned our jurisdiction on the actual rejection of Nostrum's application, not the mere existence of disagreement over a scientific issue in the course of the agency's consideration.

Beyond that, the disagreement does not seem to be cemented. In motions for extensions of briefing deadlines, Nostrum advised this court that it continued to push the FDA for relief and saw at least some prospect that it would be

successful, explaining that if the FDA "respond[ed] favorably" to the points raised in Nostrum's March letter, that would cause "Nostrum's request for review * * * [to] become moot[.]" Nostrum Mot. to Extend Deadline for Filing Brs. 2; *accord* Nostrum Emergency Mot. to Extend Deadlines for Filing Brs. 2 ("FDA's anticipated response [to the March letter] may moot this case[.]"). That Nostrum has been pursuing relief simultaneously before the agency and this court shows that the complete response letter was not a conclusive rejection of its (concededly still-pending) application. *Cf. Bellsouth Corp. v. FCC*, 17 F.3d 1487, 1489 (D.C. Cir. 1994) ("[A]n agency action cannot be considered nonfinal for one purpose and final for another.").

Nostrum's additional arguments cannot overcome the plain statutory barrier to our review.

First, Nostrum argues that, after a complete response letter issues, there is "nothing else for the agency to do." Nostrum Reply Br. 26. That is wrong. Unless the applicant voluntarily withdraws its application, the FDA will either need to consider a resubmitted application, 21 C.F.R. § 314.110(b)(1), or, if the applicant chooses not to make the suggested changes and seeks a hearing, decide on the application as it stands, *id.* §§ 314.110(b)(3); 314.200.

Second, Nostrum contends that, because it "will not voluntarily make the changes" called for in the complete response letter, the FDA "has effectively determined that the application cannot be approved" and further proceedings would be futile. Nostrum Reply Br. 27; *see id*. at 30. Not so. The regulations expressly provide that the applicant can seek a hearing at this juncture and that the FDA could then approve the application as is, without Nostrum making any changes. 21 C.F.R. § 314.110(b)(3). Or Nostrum could go forward with a

hearing, which could lead to a final FDA decision approving or rejecting the application in its current form. *See id.*; *id.* § 314.200.

Finally, Nostrum observes that the Act does not require it to request a hearing before seeking judicial review. True enough. But it does condition judicial review on the issuance of an order rejecting an application. 21 U.S.C. § 355(h). That has not happened yet.

B

For similar reasons, the FDA's denial of Nostrum's reconsideration request is not properly before us. Nostrum asked the division to reclassify the defects in its application as "minor" rather than "major[.]" J.A. 619. The denial of that request certainly is not an "order of the Secretary refusing * * * approval of an application[.]" 21 U.S.C. § 355(h).

III

Nostrum's petition for review is dismissed. Nostrum's motion to supplement the record and the FDA's separate motion to dismiss the petition are denied as moot.

So ordered.