United States Court of Appeals

FOR THE DISTRICT OF COLUMBIA CIRCUIT

Argued April 17, 2025 Decided September 26, 2025

No. 24-5235

NOVARTIS PHARMACEUTICALS CORPORATION,
APPELLANT

v.

ROBERT F. KENNEDY, JR., IN HIS OFFICIAL CAPACITY AS SECRETARY OF HEALTH AND HUMAN SERVICES, ET AL.,
APPELLEES

Appeal from the United States District Court
for the District of Columbia
(No. 1:24-cv-02234)

Catherine E. Stetson argued the cause for appellant. With her on the briefs were *Susan M. Cook* and *Marlan Golden*.

Caroline W. Tan, Attorney, U.S. Department of Justice, argued the cause for appellees. With her on the brief were *Brett A. Shumate*, Acting Assistant Attorney General, and *Daniel Tenny*, Attorney.

Chad A. Landmon argued the cause for intervenors in support of appellees. With him on the brief were *Kendall Gurule* and *Suzanne E. Bassett.*

Before: MILLETT, KATSAS, and WALKER, *Circuit Judges*.

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

KATSAS, *Circuit Judge*: Novartis Pharmaceuticals Corporation markets a drug called "Entresto," which is used to treat chronic heart failure. MSN Pharmaceuticals, Inc. filed an abbreviated new drug application to market a generic version of Entresto. The application carved out specific methods of using Entresto protected by Novartis's live patents, and it claimed that the generic drug has the same active ingredients as Entresto. The Food and Drug Administration approved the application. Novartis contends that the approval was unlawful. The district court disagreed, as do we.

I

Section 505 of the Federal Food, Drug, and Cosmetic Act (FDCA) prohibits the sale in interstate commerce of any "new drug" without prior approval by the Secretary of Health and Human Services. 21 U.S.C. § 355(a). For certain drugs, such as the generic versions of approved brand-name counterparts, the FDCA authorizes approval through an "abbreviated new drug application" (ANDA), which is substantially less onerous than the regular approval process. *Id*. § 355(j); *see Caraco Pharm. Labs., Ltd. v. Novo Nordisk A/S*, 566 U.S. 399, 404–05 (2012). The regular approval process requires studies showing that the new drug is safe and effective when used as instructed on its label. 21 U.S.C. § 355(b)(1)(A)(i), (vi). In contrast, the ANDA approval process turns on whether the new drug is sufficiently similar, across multiple dimensions, to a drug previously approved and listed under the statute. *Id.* § 355(j)(2).

Most fundamentally, the ANDA process requires the new drug to have the same "active ingredients" as those in a

previously approved drug. 21 U.S.C. § 355(j)(2)(A)(ii). Implementing regulations define an "[a]ctive ingredient" as "any component that is intended to furnish pharmacological activity." 21 C.F.R. § 314.3(b). They further state that an "identical active drug ingredient" is "the same salt or ester of the same therapeutic moiety." *Id.* And they define "[a]ctive moiety" as the part of the molecule "responsible for the physiological or pharmacological action of the drug." *Id.* Given these various definitions, the parties agree that the drug specified in an ANDA must contain the same salt or ester of the same therapeutic moiety as a previously approved drug.

For approval through an ANDA, the "labeling proposed for the new drug" generally must be "the same as the labeling approved for the listed drug." 21 U.S.C. § 355(j)(2)(A)(v). However, the statute allows "changes required … because the new drug and the listed drug are produced or distributed by different manufacturers." *Id.* FDA regulations explain that such changes may include "omission of an indication or other aspect of labeling protected by patent." 21 C.F.R. § 314.94(a)(8)(iv).[1] But such changes may not "render the proposed drug product less safe or effective than the listed drug for all remaining, nonprotected conditions of use." *Id.* § 314.127(a)(7).

These provisions often come into play when the patent for an approved drug has expired, but its manufacturer still holds patents on "some approved methods of using the drug." *Caraco*, 566 U.S. at 406. In that circumstance, a generic manufacturer may seek approval through an ANDA to "market the drug for one or more methods of use not covered by the brand's patents." *Id.* And subject to the regulations noted above, the FDA may approve a "modified label" that "'carves

[1] An "indication" is a particular medical condition that a drug is approved to address. *See* 21 C.F.R. § 314.53(b)(1).

out' from the brand's approved label the still-patented methods of use." *Id*.

II

Novartis markets Entresto, a drug widely used to treat chronic heart failure. According to its label, Entresto "contains a complex comprised of anionic forms of sacubitril and valsartan, sodium cations, and water molecules." J.A. 49.

Novartis currently holds four method-of-use patents related to Entresto. One of them covers a modified dosing regimen for patients not taking angiotensin-converting enzyme inhibitors ("ACE inhibitors") or angiotensin II receptor blockers ("ARBs"), which are other drugs used to treat heart failure. J.A. 336–37. The modified regimen calls for these patients to start by taking half the normal dose of Entresto and then gradually increase the dosage over time. Entresto's label includes the modified dosing regimen covered by this patent. Novartis's other three method-of-use patents cover use of the drug to treat patients with a preserved (as opposed to reduced) ejection fraction, which is a measure of how well the heart is contracting.

The FDA initially approved Entresto in 2015. At first, its approved use was limited to patients with chronic heart failure and a reduced ejection fraction. Novartis then conducted a clinical study involving patients with preserved ejection fractions. In 2021, the FDA approved updated labeling that indicated treatment for patients with chronic heart failure generally. The updated label added new language stating that Entresto's benefits are "most clearly evident" in patients with a reduced ejection fraction and advising doctors to "use clinical judgment in deciding whom to treat." J.A. 41.

In 2019, MSN Pharmaceuticals submitted an ANDA seeking approval to market a generic version of Entresto. MSN's proposed label omitted Novartis's patented dosing regimen for patients not taking ACE inhibitors or ARBs. Like Entresto's original label, it stated an indication for chronic heart failure with a reduced ejection fraction, thus avoiding Novartis's patented indication for use in patients with a preserved ejection fraction. The proposed label also stated that the generic drug "contains anionic forms of sacubitril and valsartan, and sodium cations." J.A. 68.

Anticipating this ANDA, Novartis filed a 2019 citizen petition asking the FDA to reject any generic version of Entresto that does not present the active ingredients—sacubitril and valsartan—"in the same chemical structure." J.A. 168–69. In 2022, Novartis filed another petition asking the FDA to reject any generic version of Entresto carving out its patented uses from the label. According to Novartis, carving out the modified dosage for patients not taking ACE inhibitors or ARBs would impermissibly render the generic version less safe and effective than Entresto. And carving out use of Entresto to treat patients with a preserved ejection fraction would require impermissibly adding words to Entresto's existing label. In 2024, the FDA denied both petitions and then approved MSN's application to market its generic alternative to Entresto.

Novartis filed this lawsuit under the Administrative Procedure Act. It seeks to set aside the FDA's denial of its citizen petitions and approval of MSN's ANDA. The parties filed cross-motions for summary judgment. The district court granted the FDA's motion and denied Novartis's. *Novartis Pharms. Corp. v. Becerra*, No. 24-cv-02234, 2024 WL 4492072 (D.D.C. Oct. 15, 2024). Novartis appealed.

III

We review a grant of summary judgment *de novo*. *AstraZeneca Pharms. LP v. FDA*, 713 F.3d 1134, 1138 (D.C. Cir. 2013). Like the district court, we must consider whether the FDA's actions were "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." 5 U.S.C. § 706(2)(A). Under this standard, a discretionary agency decision must be "reasonable and reasonably explained." *FCC v. Prometheus Radio Project*, 592 U.S. 414, 423 (2021). We review *de novo* the FDA's construction of the governing statute. *Loper Bright Enters. v. Raimondo*, 603 U.S. 369, 412 (2024). However, we afford deference to the FDA's assessment of relevant scientific questions. *Rempfer v. Sharfstein*, 583 F.3d 860, 867 (D.C. Cir. 2009).

On appeal, Novartis contends that the FDA (1) approved labeling for the new, generic drug that impermissibly deviates from the Entresto label and (2) unreasonably concluded that the generic drug has the same active ingredients as Entresto.

IV

The FDCA generally requires the labeling for a generic drug to be "the same" as that of its listed counterpart, but it permits "changes required … because the new drug and the listed drug are produced or distributed by different manufacturers." 21 U.S.C. § 355(j)(2)(A)(v). Such changes include those made to accommodate active patents on certain uses of the drug. 21 C.F.R. § 314.94(a)(8)(iv); *see Caraco*, 566 U.S. at 406. Here, all parties agree that the changes were required to avoid infringement of Novartis's patents. Novartis contends that the changes are nonetheless unlawful.

A

The first contested labeling change concerns omission of the modified dosing regimen for patients not taking ACE inhibitors or ARBs. Novartis objects that this omission renders the generic version "less safe or effective" than Entresto itself, in violation of 21 C.F.R. § 314.127(a)(7).

The FDA addressed this issue in denying Novartis's 2022 citizen petition. It found that omitting the modified dosing regimen "would not render [generic] drugs less safe or effective than Entresto." J.A. 354. The agency gave two reasons for this conclusion. First, the evidence supporting the modified dosing regimen was limited: It consisted of a single, "uncontrolled" titration study, which suggested that patients not taking ACE inhibitors or ARBs "*might*" have fewer side effects if Entresto were administered with a lower initial dose that would be gradually increased as tolerability improved over time. *Id.* at 355 (emphasis in denial order). The FDA concluded that this study did "not provide a scientific basis to conclude" that the standard Entresto dosing regimen would put any patients "at a greater risk of adverse reactions." *Id.* at 356. Second, the FDA stressed that the risk of adverse reactions could be "adequately managed" through warnings, which appear on the label of both Entresto and the generic. *Id.* at 356–57. This analysis turns squarely on the FDA's expertise in evaluating the clinical significance of drug studies, which we will not lightly second-guess. *See Rempfer*, 583 F.3d at 867.

Novartis objects that the FDA's analysis in allowing the generic drug to omit the modified dosage regimen from its label cannot be reconciled with its approval of the regimen for Entresto itself. Both decisions rested on the same titration study. According to Novartis, either the results of that study were robust enough to require inclusion of the modified

regimen on both labels, or its results were inconclusive enough to foreclose the inclusion on either label. Novartis is incorrect about how the governing legal standards fit together. An initial determination that Entresto is "safe" and "effective" with the modified dosing regimen, 21 U.S.C. § 355(b)(1)(A)(i), does not foreclose a later determination that the generic equivalent is not "less safe or effective" without it, 21 C.F.R. § 314.127(a)(7). Moreover, the FDA's assessment of the titration study has not changed over time. In approving the modified regimen for Entresto, the FDA concluded the study "suggests" that patients not taking ACE inhibitors or ARBs "might" benefit from a reduced risk of adverse effects. J.A. 331 & n.83 (FDA determination that "Novartis's proposed titration scheme *seems* reasonable and a longer titration period with a starting dose of 50mg twice daily *may* reduce the risk of" certain side effects "in patients previously on a low dose" of an ACE inhibitor or ARB (cleaned up)); *see also id.* at 132, 221. The FDA further hedged in noting that Novartis's titration study included a "small number of subjects" which "limit[ed] certain interpretation[s] of the data." *Id.* at 356 n.182. And it characterized the modified regimen not as the safest one, but as merely one with "an acceptable safety profile." *Id.* at 357 n.186. In sum, the FDA has always viewed the titration study with a degree of skepticism, despite the prior approval, so there is no unexplained change in the agency's position.

B

The second labeling change at issue concerns a difference in indications. The Entresto label states that the drug "is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in adult patients with chronic heart failure. Benefits are most clearly evident in patients with left ventricular ejection fraction (LVEF) below normal." J.A. 41. The MSN label states that its generic tablets "are indicated

to reduce the risk of cardiovascular death and hospitalization for heart failure in adult patients with chronic heart failure and reduced ejection fraction." *Id.* at 67. Both parties agree that the difference prevents the generic drug from infringing on Novartis's patent over use of the drug to treat heart failure in patients with a preserved ejection fraction.

Novartis contends that the altered indication impermissibly tracks the original, superseded Entresto label, which had an indication only for patients with a reduced ejection fraction. But in reviewing MSN's proposed label for the generic drug, the FDA plainly compared it to Entresto's current label. *See Novartis*, 2024 WL 4492072, at *7. And as the FDA explains, it is entirely unsurprising that the label for a generic drug would resemble a superseded version of the label for its listed counterpart when the manufacturer of the brand-name drug has secured a change in its label to *add* a patent-protected use. In that circumstance, the generic's tracking the unamended label reflects the intended operation of a scheme that permits the generic's label to contain changes required because the brand-name drug and the generic equivalent are sold "by different manufacturers." 21 U.S.C. § 355(j)(2)(A)(v). As explained above, those changes include "omission of an indication … protected by patent." 21 C.F.R. § 314.94(a)(8)(iv).

Novartis further objects that the indication for the generic drug unlawfully added language, whereas the regulation allows only omissions. What the regulation allows is the omission "of an *indication*," 21 C.F.R. § 314.94(a)(8)(iv) (emphasis added), and that is precisely what the labeling change at issue here accomplishes. The Entresto label indicates use for "heart failure in adult patients with chronic heart failure," thus encompassing patients with preserved and reduced ejection fractions. J.A. 41. The generic label indicates use for "heart

failure in adult patients with chronic heart failure and reduced ejection fraction." *Id.* at 67. This label adds four words, but does so to eliminate the patent-protected use of the drug to treat patients with a preserved ejection fraction. Again, that is how this scheme is supposed to work; an ANDA applicant may "propose labeling for the generic drug that 'carves out' from the brand's approved label the still-patented methods of use." *Caraco*, 566 U.S. at 406.

V

Finally, Novartis challenges the FDA's finding that Entresto and the MSN generic have the same active ingredients. This turns on whether the drugs contain the same "salt" of the same "therapeutic moiety." *See* 21 C.F.R. § 314.3(b). A "therapeutic moiety" is the part of a molecule that causes the drug's "physiological or pharmacological action." *Id.* And a "salt" is a chemical compound comprised of an anion (a negatively-charged atom or group of atoms) and a cation (a positively-charged atom or group of atoms), linked by an ionic bond. *See Novartis*, 2024 WL 4492072, at *2 n.1.

In denying Novartis's 2019 citizen petition, the FDA explained its view that the active ingredients of Entresto are sacubitril sodium and valsartan disodium, J.A. 161, which are anionic forms of sacubitril and valsartan, respectively, bonded to sodium cations, *id.* at 142–43. Novartis disputes that those are the active ingredients of Entresto. Specifically, Novartis contends that Entresto does not contain sacubitril sodium and valsartan disodium *as separate salts*. Novartis points to Entresto's label, which reveals that the drug "contains a *complex* comprised of anionic forms of sacubitril and valsartan

[and] sodium cations." *Id.* at 49 (emphasis added).[2] According to Novartis, the presence of this "complex" distinguishes Entresto from MSN's generic drug which, according to its label, "contains anionic forms of sacubitril and valsartan, and sodium cations" but not a complex. *Id.* at 68. Along the same lines, Novartis points to the FDA's original approval of Entresto, which described the drug as containing a "co-crystal … consisting of" sacubitril and valsartan anions and sodium cations. FDA Ctr. for Drug Evaluation & Rsch., *Office Director Decisional Memo on NDA No. 207620* at 2 (July 7, 2015).

We are not persuaded. For one thing, longstanding FDA regulations and guidance make clear that drugs can have the same active ingredients even if they have different solid-state physical forms or crystal structures. *See* Final Rule: Abbreviated New Drug Application Regulations, 57 Fed. Reg. 17,950, 17,959 (Apr. 28, 1992) (only in "some cases" would the FDA specify that "crystalline structure" is material to an ingredient's sameness); FDA, *Guidance for Industry: ANDAs: Pharmaceutical Solid Polymorphisms* 5–6 (July 2007). For another, the FDA convincingly applied that principle in rejecting Novartis's request to require generic drugs to have the same co-crystal structure as Entresto. In essence, the FDA reasoned that the co-crystal structure has nothing to do with Entresto's chemical composition or its pharmacological effects. The FDA explained that, in Entresto's co-crystal structure, the sacubitril sodium and valsartan disodium molecules "are not ionically bound" to one another. J.A. 143. Moreover, the co-crystal "dissociates rapidly in vivo to sacubitril and valsartan," so "there is no systemic exposure" to

[2] According to the FDA, a "complex" is a combined molecular entity "formed by loose association involving two or more molecular entities." J.A. 142 n.7 (cleaned up).

it. *Id.* at 143–44. And there is no evidence "demonstrating that the physical form of the active ingredients in Entresto is known to impact the safe or effective use of the drug." *Id.* at 159. Novartis's objection gives us no reason to question the FDA's expert judgment regarding these scientific issues.

Affirmed.