United States Court of Appeals

FOR THE DISTRICT OF COLUMBIA CIRCUIT

Argued November 7, 2022 Decided January 10, 2023

No. 22-5202

SANDOZ INC.,
APPELLANT

v.

XAVIER BECERRA, 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. 1:21-cv-00600)

William M. Jay argued the cause for appellant. With him on the briefs were *Brian T. Burgess* and *Gerard J. Cedrone*. *Michael D. Shumsky* entered an appearance.

Steven H. Hazel, Attorney, U.S. Department of Justice, argued the cause for appellees. With him on the brief were *Brian M. Boynton*, Principal Deputy Assistant Attorney General, *Daniel Tenny*, Attorney, *Samuel Bagenstos*, General Counsel, U.S. Department of Health and Human Services, and *Leslie R. Cohen*, Associate Chief Counsel, U.S. Food and Drug Administration.

Before: MILLETT, PILLARD and RAO, *Circuit Judges*.

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

RAO, *Circuit Judge*: Under the Hatch-Waxman Act, a drug may receive "new chemical entity exclusivity" if no active ingredient in the drug was previously "approved." The drug Aubagio was awarded this exclusivity because the Food & Drug Administration ("FDA") determined that Aubagio's only active ingredient, teriflunomide, had never previously been approved. This case concerns a challenge to Aubagio's exclusivity period, which Sandoz Inc. raises to secure a solo period of marketing exclusivity for its generic equivalent. Sandoz maintains that teriflunomide was previously "approved" as an impurity in the drug Arava. In the alternative, Sandoz argues that teriflunomide was in fact approved as an active ingredient in Arava. The district court granted summary judgment for the FDA, agreeing with the agency that Aubagio was entitled to exclusivity because teriflunomide had never previously been approved.

We affirm the judgment of the district court. Although Sandoz did not exhaust its statutory argument before the FDA, in the absence of a statutory or regulatory exhaustion requirement, we find it appropriate to decide Sandoz's challenge. When the FDA approves a new drug, it does not also "approve" known impurities in that drug for the purpose of new chemical entity exclusivity. And the record is clear the FDA did not approve teriflunomide as an active ingredient when it approved Arava. Aubagio was therefore entitled to new chemical entity exclusivity, and Sandoz cannot benefit from a solo exclusivity period for its generic equivalent.

I.

A.

Before a new drug may be sold or marketed in the United States, it must be approved by the FDA. Typically, drug sponsors submit a "new drug application," or "NDA," to the agency under section 505(b) of the Federal Food, Drug, and Cosmetic Act ("FDCA"). *See* FDCA, Pub. L. No. 75-717, § 505(b), 52 Stat. 1040, 1052 (1938) (codified as amended at 21 U.S.C. § 355(b)). A new drug applicant must submit reports of trials showing the drug is both safe and effective. *See* 21 U.S.C. § 355(b)(1).

In the Hatch-Waxman Act, Congress amended the FDCA to provide a more streamlined path for the approval of generic drugs. Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, tit. I, § 101, 98 Stat. 1585, 1585 (codified as amended at 21 U.S.C. § 355(j)). Generic drugs are those that "contain[] the same active ingredients but not necessarily the same excipients as a so-called 'pioneer drug' that is marketed under a brand name." *United States v. Generix Drug Corp.*, 460 U.S. 453, 454–55 (1983). Instead of following the rigorous NDA process, generic manufacturers may file an "abbreviated new drug application," or "ANDA." In the abbreviated process, a manufacturer may bypass the safety and efficacy demonstrations required for a new drug by showing its generic drug contains the same active ingredient as a previously approved drug and is equivalent in other respects. *See* 21 U.S.C. § 355(j)(2)(A).

The Hatch-Waxman Act made it easier to get approval for generics, but also preserved incentives for the research and innovation necessary for the development of new drugs. *See Abbott Labs. v. Young*, 920 F.2d 984, 985 (D.C. Cir. 1990). Manufacturers who developed novel drugs would enjoy

specified terms of marketing exclusivity. The most generous such term—and the one at issue in this case—is known as "new chemical entity exclusivity," which applies when "an application submitted under subsection (b) of this section for a drug, no active ingredient … of which has been approved in any other application under subsection (b) of this section, is approved."[1] 21 U.S.C. § 355(j)(5)(F)(ii). Applications "submitted under subsection (b) of this section" are NDAs. In other words, new chemical entity exclusivity applies when a new drug is approved and no active ingredient in that drug was previously "approved" in a different drug.

This case implicates a four-year term of new chemical entity exclusivity because Sandoz filed an ANDA that contained a "paragraph IV certification," which challenges a patent of a previously approved drug.[2] The first generic manufacturer to file such an application enjoys a 180-day

---

[1] Since the events at issue in this case, the FDCA has been amended to use the phrase "active moiety" rather than "active ingredient." *See* Act to Amend the Federal Food, Drug, and Cosmetic Act, Pub. L. No. 117-9, § 1(a)(1)(B), 135 Stat. 256, 256 (2021). The parties agree the distinction is not material in this case. This opinion refers to "active ingredient," the statutory term at the time of the agency decisions under review, and to the version of section 505 in force on September 12, 2012, the date the FDA awarded new chemical entity exclusivity to Aubagio.

[2] If a manufacturer wishes to market a generic drug before one of the patents on the underlying drug expires, it must certify "that such patent is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted." 21 U.S.C. § 355(j)(2)(A)(vii)(IV). This is the "paragraph IV certification" involved here. A new chemical entity will receive five years of exclusivity against generic competitors that do not challenge any of the patents associated with the drug. *See id.* § 355(j)(5)(F)(ii).

period of exclusivity.[3] *See* 21 U.S.C. §§ 355(j)(5)(B)(iv)(I), (II)(bb). Under the new chemical entity regime, ANDAs may not be submitted for generics before the end of the four-year exclusivity period. *Id.* § 355(j)(5)(F)(ii). Since multiple applicants often submit ANDAs on exactly that date, the 180-day period of marketing exclusivity will often be shared among generic manufacturers who all qualify as "first applicant[s]." *See id.* § 355(j)(5)(B)(iv).

B.

Sandoz, a generic manufacturer, sought approval for a generic corresponding to the drug Aubagio. Aubagio has teriflunomide as its sole active ingredient and is used to treat patients with relapsing multiple sclerosis. When the FDA approved Aubagio on September 12, 2012, it determined that it had not previously approved teriflunomide in any other drug and that Aubagio was eligible for new chemical entity exclusivity. Accordingly, generic manufacturers could not submit ANDAs corresponding to Aubagio until September 12, 2016. But Sandoz sought to challenge the exclusivity period and so moved sooner. It submitted a letter to the FDA on August 31, 2016, arguing that the agency had previously approved teriflunomide and that Aubagio was therefore ineligible for new chemical entity exclusivity.[4]

---

[3] Because a paragraph IV certification qualifies as an act of patent infringement, *see* 35 U.S.C. § 271(e)(2)(A), this exclusivity provision serves to "compensate manufacturers for research and development costs as well as the risk of litigation from patent holders," *Teva Pharms., USA, Inc. v. Leavitt*, 548 F.3d 103, 104 (D.C. Cir. 2008).

[4] Under Sandoz's view, Aubagio may have been eligible for a lesser three-year term of exclusivity that applies when a new drug uses the

Sandoz's letter focused on a rheumatoid arthritis drug known as Arava, which the FDA approved in 1998. Arava uses leflunomide, which the FDA identified as the sole active ingredient in the drug. When Arava is manufactured and stored, however, some of the leflunomide molecules break down into teriflunomide, a similar compound. The FDA characterized teriflunomide as an "impurity" and allowed Arava to contain up to 3.5 percent teriflunomide. In its letter, Sandoz argued that the small quantities of teriflunomide that build up in Arava contribute to the functioning of the drug, and that teriflunomide was "physically present as a bioavailable and physiologically/pharmacologically active component" of Arava. Sandoz contended that the FDA had "approved" teriflunomide when it approved Arava and therefore that the FDA should rescind new chemical entity exclusivity for Aubagio, which used teriflunomide as its active ingredient.

While the FDA considered Sandoz's request to rescind Aubagio's exclusivity, Sandoz submitted two ANDAs for its generic teriflunomide product, each with a paragraph IV certification: one on September 7, 2016, in advance of the four-year deadline, and one on September 12, 2016, the day the deadline expired.

Whether Sandoz would enjoy sole exclusivity, or would share exclusivity with other manufacturers, hinged on the FDA's determination of whether Aubagio was properly classified a new chemical entity. Because Sandoz was the only generic manufacturer to file a substantially complete ANDA prior to the four-year deadline, it would qualify as the only first applicant should the FDA rescind Aubagio's four-year exclusivity term. Sandoz would thus enjoy 180 days of sole

---

active ingredient in a previously approved drug but repurposes it for a new use. *See* 21 U.S.C. § 355(j)(5)(F)(iii).

exclusivity. Conversely, if the FDA rejected Sandoz's request, the first ANDA would be premature and Sandoz would share first applicant status with some twenty generic applicants who all filed on September 12, 2016, obviously limiting the value of the exclusivity period.[5]

In June 2018, the FDA rejected Sandoz's request to rescind Aubagio's new chemical entity exclusivity. Under the agency's longstanding interpretation of the exclusivity provisions, an ingredient is "approved" in a new drug application only if it was an active ingredient in that drug. The agency concluded it had recognized teriflunomide simply as an impurity in Arava, not as an active ingredient. As the FDA explained, leflunomide was the sole active ingredient in Arava. The safety and efficacy studies had focused on leflunomide, and nothing in Arava's application indicated that the presence of teriflunomide as a degradant was designed to serve a therapeutic function. Because Aubagio was properly granted a four-year period of exclusivity, the FDA rejected Sandoz's first ANDA as premature.

In an administrative appeal, Sandoz argued that Arava was a "combination drug product containing both leflunomide and teriflunomide" as active ingredients. The FDA denied this appeal on February 12, 2021, affirming its prior reasoning and again concluding that leflunomide was the only active ingredient approved in Arava.

---

[5] While Aubagio's term of exclusivity has since expired, the validity of that term remains relevant because no manufacturer has marketed a generic corresponding to Aubagio and triggered the 180-day exclusivity provision. Sandoz explains that this is because Aubagio's sponsor, Sanofi-Aventis, has granted licenses for generic manufacturers to enter the U.S. market on March 12, 2023. This opinion has been prepared on an expedited basis to reflect that date.

C.

Sandoz filed suit under the Administrative Procedure Act in the U.S. District Court for the District of Columbia, alleging the FDA's decision to maintain new chemical entity exclusivity for Aubagio was "not in accordance with law." 5 U.S.C. § 706(2)(A).[6]

Sandoz challenged the FDA's interpretation of the exclusivity provisions, arguing the FDA had misinterpreted the FDCA in determining that an ingredient was "approved" only if it was the active ingredient in some previously approved drug. Sandoz emphasized the grammar of the exclusivity provision, and its reference to the approval of "an application submitted under subsection (b) of this section for a drug, no active ingredient … of which has been approved in any other application under subsection (b) of this section." 21 U.S.C. § 355(j)(5)(F)(ii). According to Sandoz, this phrase requires the FDA to determine whether the active ingredient in the new drug is the same as *any known substance*, whether an active ingredient or an impurity, in a previously approved drug. Even if the FDA correctly concluded teriflunomide was only an impurity in Arava, on Sandoz's understanding, the FDA necessarily approved that impurity, and Aubagio is therefore ineligible for new chemical entity exclusivity. In the alternative, Sandoz maintained that teriflunomide was present as an active ingredient in Arava because its presence as a degradant was therapeutically useful.

The district court granted summary judgment for the Government. As to Sandoz's statutory argument, the district court determined the phrase "no active ingredient … of which

[6] Sandoz also argued the FDA's decision was arbitrary and capricious, but it does not press that argument on appeal.

has been approved" was most naturally read to mean "approved *as an active ingredient*" and not merely as an impurity. The district court agreed with the FDA that teriflunomide was not an active ingredient in Arava, and that the agency had not approved it as such. Sandoz timely appealed the district court's grant of summary judgment, which we review de novo. *See Rempfer v. Sharfstein*, 583 F.3d 860, 864–65 (D.C. Cir. 2009).

II.

We begin with Sandoz's statutory argument that when the FDA approves a new drug it "approve[s]" known impurities in that drug. Under this reasoning, Aubagio was not entitled to exclusivity because its active ingredient was teriflunomide, which already had "been approved" in Arava as an impurity. Although Sandoz did not explicitly raise this issue before the FDA, in the absence of any statutory or regulatory exhaustion requirement, we find it appropriate to decide Sandoz's arguments. On the merits, we uphold the FDA's interpretation because it is consistent with the text and structure of the FDCA.

A.

The Government contends that Sandoz failed to exhaust its statutory challenge before the FDA. Although the district court did not address exhaustion, we address it here, because the Government is correct that Sandoz did not raise this argument before the agency.

In its letters to the FDA, Sandoz did not contest the agency's well-established interpretation that a new drug that utilizes an ingredient previously identified only as an impurity may be eligible for new chemical entity exclusivity. Sandoz simply argued that teriflunomide had been approved as an active ingredient, not merely an impurity, in Arava. Shortly before the FDA issued its final decision on Sandoz's

administrative appeal, Sandoz shared with the agency a draft complaint that we are told resembles the one ultimately filed in the district court. But Sandoz did not explicitly ask the agency to revisit its statutory conclusion, nor did it request that the FDA take time to review the arguments raised in the complaint. In district court, Sandoz argued for the first time that the FDA had erroneously interpreted the statute. We agree with the Government that simply sharing a draft complaint at the very end of a lengthy administrative process—without even requesting the agency consider the arguments raised in that complaint—does not "reasonably flag[]" an issue "for the agency's consideration." *NTCH, Inc. v. FCC*, 841 F.3d 497, 508 (D.C. Cir. 2016) (cleaned up).

In this case, however, the Government identifies no applicable statutory or regulatory exhaustion requirement, and we are not aware of one. As the Supreme Court has explained, "requirements of administrative issue exhaustion are largely creatures of statute," and the Court's "cases addressing issue exhaustion reflect this fact." *Sims v. Apfel*, 530 U.S. 103, 107–08 (2000). In some circumstances, courts may apply a "judicially imposed issue-exhaustion requirement." *Id.* at 108. But in the absence of a legal exhaustion requirement, the "administrative-waiver doctrine does not represent an ironclad rule." *Advocs. for Highway & Auto Safety v. Fed. Motor Carrier Safety Admin.*, 429 F.3d 1136, 1148 (D.C. Cir. 2005).

This court has recognized that as a prudential matter we may "exercise our discretion to address" an issue not exhausted before the agency. *R.R. Yardmasters of Am. v. Harris*, 721 F.2d 1332, 1337 (D.C. Cir. 1983); *see also Okla. Dep't of Env't Quality v. EPA*, 740 F.3d 185, 192 (D.C. Cir. 2014) (considering on the merits an issue not raised before the Environmental Protection Agency). When determining whether to exercise such discretion, we must heed the Supreme

Court's caution that courts should not apply judicial issue exhaustion without considering the particulars of an administrative scheme. Prudential issue exhaustion arises out of "an analogy to the rule that appellate courts will not consider arguments not raised before trial courts," and we must not "reflexively assimilat[e] the relation of administrative bodies and the courts to the relationship between lower and upper courts." *Sims*, 530 U.S. at 108–09, 110 (cleaned up). Recently, in *Carr v. Saul*, the Supreme Court reiterated that whether a court should impose an issue exhaustion requirement "depends on the degree to which the analogy to normal adversarial litigation applies in a particular administrative proceeding." 141 S. Ct. 1352, 1358 (2021) (quoting *Sims*, 530 U.S. at 109).

In *Sims* and *Carr*, the Supreme Court declined to impose exhaustion in the context of highly structured procedures adopted by the Social Security Administration involving review before administrative adjudicators. *See Carr*, 141 S. Ct. at 1356 (involving a hearing before an administrative law judge); *Sims*, 530 U.S. at 105 (involving review of an administrative law judge's decision by the Social Security Appeals Council); 20 C.F.R § 404.900 (explaining the six-step administrative review process at issue in both cases). The Court declined to impose issue exhaustion because it concluded that these procedures were not similar enough to adjudication in lower courts. More generally, the Court has noted that determining whether to require administrative exhaustion is "intensely practical" and turns on "both the nature of the claim presented and the characteristics of the particular administrative procedure provided." *McCarthy v. Madigan*, 503 U.S. 140, 146 (1992) (cleaned up) (discussing these principles in the context of administrative remedies).

Applying these considerations, we see no reason to treat Sandoz's statutory argument as forfeited. First, the proceedings

here were far from adversarial. Sandoz submitted letters to the FDA challenging the new chemical entity exclusivity that had been awarded years earlier to Arava. While Sanofi-Aventis, Aubagio's sponsor, also sent a letter to the FDA defending its exclusivity, the letters were simply considered under the FDA's internal review procedures, which are governed by nonbinding guidance documents. Formal Dispute Resolution: Sponsor Appeals Above the Division Level at 1–2, https://www.fda.gov/media/126910/download (Nov. 2017) (providing procedures for internal agency appeals that "do not establish legally enforceable responsibilities"). The FDA's review involved no adjudicator, but rather determinations by counsel in the Office of Regulatory Policy and by the Director for the Office of Generic Drugs.

The FDA's informal process for reviewing such letters before agency officials cannot be analogized to "normal adversarial litigation," involving "a litigant opposing the claimant." *Carr*, 141 S. Ct. at 1358, 1359 (cleaned up). The FDA's procedures are entirely distinct from those cases in which the Supreme Court has found issue exhaustion appropriate, all of which involved a quasi-judicial process conducted between adverse parties before a neutral examiner.[7]

[7] For instance, *Hormel v. Helvering* concerned a proceeding before the Board of Tax Appeals, where the petitioner and the Commissioner of Internal Revenue presented separate arguments to the Board. *See* 312 U.S. 552, 553–54 (1941); *see also Blair v. Oesterlein Mach. Co.*, 275 U.S. 220, 225 (1927) (same). *Unemployment Compensation Commission of Alaska v. Aragon* involved a proceeding before a hearing examiner who similarly took testimony from adverse parties. *See* 329 U.S. 143, 147–48 (1946); *Aragon v. Unemployment Comp. Comm'n of Alaska*, 149 F.2d 447, 450–52 (9th Cir. 1945). And *United States v. L.A. Tucker Truck Lines, Inc.* concerned a proceeding before the Interstate Commerce Commission, where the hearing examiner was tasked solely with

The FDA's review is also far less formal than the multi-step regulatory process in the Social Security context, which the Court found insufficiently adversarial in *Sims* and *Carr*. In short, the proceedings before the FDA do not support the "'analogy to judicial proceedings' that undergirds judicially created issue-exhaustion requirements." *Carr*, 141 S. Ct. at 1360 (quoting *Sims*, 530 U.S. at 112 (plurality opinion)).

Second, as to the nature of Sandoz's claim, it is a question of law on which the agency's views have been fully articulated before the district court and in the briefs and arguments before this court. Moreover, the resolution of this dispute does not "require the development of a factual record." *Yardmasters*, 721 F.2d at 1338.

In the circumstances here, Sandoz's failure to present the issue to the agency does not bar adequate consideration by this court. Review of Sandoz's legal arguments is appropriate, and we decline to impose an exhaustion requirement.

B.

Considering the text and structure of the FDCA, we hold that when the FDA approves a new drug, known impurities in that drug have not "been approved" within the meaning of the statute. Therefore, a new drug that employs a known impurity as its active ingredient is eligible for new chemical entity exclusivity.[8] Aubagio employs a known impurity—

"decid[ing] justly between contestants in an adversary proceeding." 344 U.S. 33, 36 (1952). These factual scenarios could not be further afield from the letter correspondence at issue here.

[8] We do not address the circumstance in which a new drug uses as its active ingredient an "inactive ingredient" identified in a previously approved drug. FDA regulations and guidance documents provide distinct definitions for inactive ingredients and impurities, as well as

teriflunomide—as the active ingredient in a new drug to treat multiple sclerosis. We agree with the FDA that because teriflunomide was only an impurity and therefore not previously "approved" in Arava, Aubagio was entitled to new chemical entity exclusivity.

1.

We begin with the text of the statute. The FDA and Sandoz disagree about whether FDA approval of a drug means the agency "has approved" known impurities in that drug, such that a later new drug that uses an impurity as its active ingredient can benefit from new chemical entity exclusivity.

New chemical entity exclusivity is granted "for a drug, no active ingredient … of which has been approved in any other" new drug application. 21 U.S.C. § 355(j)(5)(F)(ii). Reading this provision in context, it is plain the FDA does not "approve" a known impurity when it approves a drug that contains that impurity. To "approve" means "[t]o sanction officially." *Approve*, BLACK'S LAW DICTIONARY (6th ed. 1990); *see also Approve, v.1*, OXFORD ENGLISH DICTIONARY (2d ed. 1989) (meaning "[t]o confirm authoritatively; to sanction"); *Approve*, MERRIAM-WEBSTER'S NINTH NEW COLLEGIATE DICTIONARY (1983) (meaning "to accept as satisfactory" or "to give formal or official sanction to").

The FDA did not approve or "sanction officially" teriflunomide when it recognized it as an impurity in Arava. When the FDA receives a new drug application, the question before the agency is whether the proposed drug meets a variety

---

different regulatory treatment. The issues presented and the parties' briefing concern only impurities. This opinion does not address the application of new chemical entity exclusivity to drugs that make use of a previously recognized inactive ingredient.

of criteria—including whether pharmacological tests reliably demonstrate the drug's efficacy and safety and whether the manufacturing process will preserve the drug's purity. *See* 21 U.S.C. § 355(d). The FDA makes a single decision whether to approve or reject the drug.

While the FDA approves the drug as a whole, assessment and study of the active ingredient is central to the new drug approval process. *See, e.g.*, 21 U.S.C. §§ 355(b)(1), j(4), (j)(5)(F)(ii), (j)(5)(F)(iii); *see also Pharmanex v. Shalala*, 221 F.3d 1151, 1156 (10th Cir. 2000) (noting that "approval of active ingredients is integral to the overall new drug approval process"). Active ingredients are those "intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease." 21 C.F.R. § 314.3(b). The approval process focuses primarily on assessing the operation and safety of such ingredients. The active ingredient must fulfill a specific pharmacological purpose as demonstrated by clinical trials. *Id.*; 21 U.S.C. § 355(d). An active ingredient is approved in a new drug only at a specified quantity and for a specified use, parameters that must be set out in the drug's label. *See* 21 U.S.C. §§ 352(e)-(f). For instance, the Arava label states the drug contains either 10, 20, or 100 milligrams of leflunomide, to be taken orally to treat active rheumatoid arthritis. The agency's review of the active ingredient is affirmative and thorough, designed to ensure that upon approval the drug will serve its intended function safely.

By contrast, the FDCA new drug approval process includes no reference to impurities at all. Instead, impurities are a category created by the agency, relating to the statutory requirement that new drug applicants list the "components" of the proposed drug. 21 U.S.C. § 355(b)(1). FDA guidance documents define an "impurity" as "[a]ny component" of the drug that is neither the active ingredient nor an "excipient."

Excipients are "inactive ingredients that are routinely and purposefully added … to enhance the performance of the active ingredient." *Glaxo Grp. Ltd. v. Apotex, Inc.*, 376 F.3d 1339, 1347 (Fed. Cir. 2004). Unlike active ingredients and excipients, impurities are not deliberately added to the drug but may "arise during the synthesis, purification, and storage of a new drug substance," when, for instance, chemicals in the drug react or degrade.

Impurities are reviewed only to assess whether the manufacturing process is "inadequate to preserve" the drug's "identity, strength, quality, and purity." 21 U.S.C. § 355(d). The FDA focuses on whether the impurity undermines the safety or efficacy of the drug but does not otherwise directly study the pharmacological effects of an impurity. The agency may tolerate low levels of impurities when approving a drug. But the limited review does not sanction or approve the impurities, some which may be benign or even beneficial and others which may in fact be toxic or carcinogenic. *See Sandoz Inc. v. Becerra*, 2022 WL 2904262, at *6 (D.D.C. July 22, 2022); Draft Guidance for Industry on Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches; Availability, 73 Fed. Reg. 76,361, 76,362 (Dec. 16, 2008) (draft guidance designed to provide "approaches for handling impurities with known genotoxic or carcinogenic potential," including "reduction of the impurity level to an acceptable threshold").

In approving a new drug, the FDA does not specify the precise amount of a given impurity that the drug must contain, only a ceiling. This makes sense because, as was the case for Arava, impurities often arise unintentionally in manufacture and storage, and the quantity of a given impurity may vary "from batch to batch" or "at different times over the shelf life" of the drug. If the impurity could be eliminated altogether from

the manufacturing process, so much the better. Whatever the variable quantity of an impurity, the FDA insists only that it does not reach a level that undermines the safety or efficacy of the drug. The statute and regulatory scheme make clear that ingredients identified as impurities are not rigorously studied for their "direct effect" in the treatment and cure of disease. Rather, the FDA ensures that any impurities arising from the drug's production and manufacture do not indirectly compromise the overall safety and efficacy of the drug and its active ingredient.

The FDA's identification of a permissible upper level of an impurity in no way suggests the impurity "has been approved" within the plain meaning of the FDCA. Therefore, we conclude that when the FDA recognized teriflunomide as an impurity in Arava, it did not approve that ingredient. The FDA properly granted new chemical entity exclusivity to Aubagio, which utilized teriflunomide as an "active ingredient" in a new drug.

This conclusion is reinforced by the "language and design of the statute as a whole." *K Mart Corp. v. Cartier, Inc.*, 486 U.S. 281, 291 (1988). To begin with, active ingredients are also central to the FDCA's approval process for generic drugs. An ANDA may be submitted only when the "active ingredient" of the proposed generic drug "is the same as that of the listed drug." 21 U.S.C. § 355(j)(2)(A)(ii). Generic drugs also must be identical to the listed drug in other ways—for instance, by having the same dosage and identical labeling. *See id.* §§ 355(j)(2)(A)(iii), (v). Yet there is no requirement that a generic drug contain the same impurities as the listed drug.

Similarly, the FDA closely regulates the labeling of drugs, but not with respect to impurities. A drug's label must disclose each active ingredient and its exact quantity, as well as a list of

each inactive ingredient, but the label need not say anything at all about impurities. *See id.* §§ 352(e)(1)(A)(ii)–(iii) (requiring the name and quantity of each active ingredient and the name of each inactive ingredient to be listed, but imposing no requirement as to impurities); 21 C.F.R. § 201.66(c) (enumerating the labeling requirements for over-the-counter drugs and making no reference to impurities); *id.* § 201.100(b) (same for prescription drugs). These provisions confirm the indirect and largely negative consideration of impurities in the FDA's approval and labeling requirements.

Granting new chemical entity exclusivity to Aubagio is also consistent with Congress's careful calibration of the terms of exclusivity. The FDCA grants a longer term of exclusivity for drugs developed with a novel active ingredient and a shorter period for drugs that utilize an already approved active ingredient for a novel use. *Compare* 21 U.S.C. § 355(j)(5)(F)(ii) (permitting new chemical entity exclusivity for four or five years when the active ingredient in the drug has never been approved), *with id.* § 355(j)(5)(F)(iii) (permitting three years of exclusivity when the active ingredient in a new drug was previously approved but the sponsor makes use of "new clinical investigations" "essential to the approval of the application").

Because Aubagio was the first drug to utilize teriflunomide as an active ingredient, the FDA properly granted four years of exclusivity. As already discussed, the evaluation of a new drug's active ingredient requires rigorous testing and safety reviews before the drug may receive approval. When a previously approved active ingredient is repurposed to a new use, the applicant and the agency will have had the benefit of prior clinical trials, a previous new drug approval process squarely focused on resolving whether the ingredient is efficacious and safe, and previous experience in

manufacturing the ingredient at a definite quantity. A manufacturer developing an impurity as an active ingredient for the first time will not have the advantage of such rigorous testing and study. After all, impurities are reviewed only for the specific purpose of determining whether their presence in a limited quantity will compromise the drug.

As the Government explains, "[i]n practice, few substances are entirely unknown," and major innovations often occur when substances are first given therapeutic use, even if the substance was previously recognized by the FDA. Therefore, identifying that an impurity serves a pharmacological benefit as an active ingredient will require additional research and testing to satisfy the FDA's rigorous approval standards. *See id.* § 355(b)(1) (requiring "full reports of investigations" to show the drug is safe and effective).

Consistent with the statutory and regulatory scheme, the development of an impurity into an active ingredient is much more like identifying a novel active ingredient than like undertaking clinical investigations to find a new use for a previously approved active ingredient. Aubagio employed a known impurity as its active ingredient and so the longer exclusivity period was appropriate.

2.

Furthermore, we note Congress has clarified the scope of new chemical entity exclusivity in a manner that reaffirms that the FDA's approval process is concerned with active ingredients and not impurities. In section 505(u) of the FDCA, Congress extended new chemical entity exclusivity to certain drugs that use part of the active ingredient in a previously approved drug. Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, tit. XI, § 1113, 121 Stat. 823, 976–77 (codified at 21 U.S.C. § 355(u)). More precisely, a

single enantiomer of a racemic mixture may be eligible for exclusivity. A racemic mixture is an equal combination of two enantiomers—molecules that are oriented as mirror images of each other, much like a person's left and right hands. *See generally* Mark A. Lemley, *Expecting the Unexpected*, 92 NOTRE DAME L. REV. 1369, 1377 (2017). Section 505(u) ensures that a drug making novel use of a single enantiomer is eligible for new chemical entity exclusivity, even if the racemic mixture was previously approved. Applicants for such a drug may "elect to have the single enantiomer not be considered the same active ingredient as that contained in the approved racemic drug" for purposes of new chemical entity exclusivity. 21 U.S.C. § 355(u)(1). This reflects the fact that a single enantiomer may be therapeutically useful in novel ways. Lemley, 92 NOTRE DAME L. REV. at 1377–78.

Section 505(u), however, is operative only if the racemic mixture was previously approved as an "active ingredient," not if the racemic mixture was only a known impurity. *See* 21 U.S.C. § 355(u)(1) (providing that the enantiomer may "not be considered the same *active ingredient* as that contained" in the previously approved racemic drug) (emphasis added). This confirms that FDA approval of a racemic drug is equivalent to approval of the active ingredient in that racemic drug.

Sandoz argues that a "racemic drug" must be a drug that has a racemic mixture as an active ingredient, so section 505(u) simply is not implicated when a racemic mixture is approved as an impurity. But Sandoz's interpretation of section 505(u), combined with its view that exclusivity is barred for a known impurity, leads to a puzzling outcome. Consider a new drug that employs an enantiomer as its active ingredient. Under Sandoz's understanding, if the racemic mixture of which the enantiomer is a part was previously recognized only as an *impurity*, the new drug would not receive exclusivity. On the

other hand, if the racemic mixture was previously approved as an *active ingredient*, the new drug using the enantiomer would be eligible for exclusivity under section 505(u).

If we accepted Sandoz's interpretation, there would be no exclusivity for researching and developing an enantiomer previously recognized as a mere impurity, yet there would be exclusivity for repurposing an enantiomer that had already been rigorously studied and approved as an active ingredient. This outcome cannot be squared with the text and structure of the FDCA, in which Congress aligned longer periods of exclusivity with greater innovation and research.

3.

Finally, we are unpersuaded by Sandoz's contrary interpretation, which would significantly constrain the scope of new chemical entity exclusivity in a manner inconsistent with the statutory scheme. Sandoz maintains that when the FDA approves a new drug, it approves all the ingredients in that drug that are known and disclosed to the FDA, including any impurities. This argument relies heavily on the grammar of the relevant statutory language. Recall that new chemical entity exclusivity is available when "an application submitted under subsection (b) of this section for a drug, no active ingredient … of which has been approved in any other application under subsection (b) of this section, is approved." 21 U.S.C. § 355(j)(5)(F)(ii). Because the relative pronoun "which" modifies "drug," Sandoz argues the only question is whether the active ingredient in the later drug was "approved" as *any ingredient* in a previously approved drug. Sandoz would deem any known impurities in the drug, along with the active ingredients, to have been approved by the FDA.

Sandoz's argument hinges on the rules of grammar. While such rules may be a useful guide to statutory meaning, they

cannot resolve meaning when divorced from the text and structure of the statute. A narrow focus on grammar fails to answer the relevant statutory question here, which is whether the FDA has "approved" an impurity when it approves a new drug containing that impurity. Our conclusion that the FDA does not in fact approve such an impurity is compelled by the language of the provision, the statutory context, and the scope of the new drug approval process implemented by the FDA through its regulations and guidance.

Sandoz suggests the FDA approves "each of the known components disclosed" in an NDA, but as we have already explained, the limited role that impurities play in the new drug approval process makes clear the FDA does not "approve" known impurities within the meaning of the statute. Sandoz's interpretation cannot be squared with the FDCA and the reality of the agency's approval process for new drugs.

* * *

In sum, the FDA does not officially sanction an impurity when it approves a drug as a whole. When the FDA concludes a particular impurity is permissible up to certain levels in an approved drug, it is merely determining that a limited quantity of the impurity will not bar the approval of a new drug. The FDA did not "approve" teriflunomide when it approved the drug Arava, and therefore Aubagio was entitled to new chemical entity exclusivity.

III.

We also reject Sandoz's alternative argument that teriflunomide in fact was an active ingredient in Arava. The record is clear that the FDA did not approve teriflunomide as such when it approved Arava. The Arava application referred to leflunomide as the only active ingredient in the drug. The

Arava approval process and efficacy review focused entirely on leflunomide. The FDA's ultimate approval was simply for "Arava (leflunomide) [t]ablets" with the label "ARAVA™ (leflunomide)." Nothing in the Arava application suggested that the variable quantity of teriflunomide as a degradant was "intended" to furnish any "pharmacological activity" or "direct effect." Instead, the application focused entirely on the therapeutic effects of leflunomide.

In light of this record, Sandoz does not suggest the FDA explicitly approved teriflunomide as an active ingredient. Instead, Sandoz argues teriflunomide met the regulatory criteria for an "active ingredient," because it is a "component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease." 21 C.F.R. § 314.3(b). Sandoz contends that the small quantity of teriflunomide that accumulates in Arava during manufacturing and storage assists in treating rheumatoid arthritis and thus falls within this definition. To support its claim, Sandoz cites to contemporaneous patent filings, which supposedly suggest Arava's sponsors believed the degradation of leflunomide into teriflunomide would assist Arava's pharmacological effects. Sandoz maintains the FDA erred in not considering teriflunomide as an active ingredient.

The FDA, however, was not required to take notice of patent filings in its review of Arava's application. In reviewing new drug applications, the FDA makes decisions "upon the basis of the information submitted … as part of the application" or otherwise "before" the agency. 21 U.S.C. § 355(d). While applications must list patents for which "a claim of patent infringement could reasonably be asserted," *see id.* § 355(b)(1), these requirements are designed to make public the patents associated with a drug, not to further the FDA's substantive review of the drug. The FDA's review of patent

information is "purely ministerial," and the statute requires the agency "to publish submitted patent information" but not "to review the merits of the patent information provided." *Teva Pharms., USA, Inc. v. Leavitt*, 548 F.3d 103, 106 (D.C. Cir. 2008). After all, the FDA has no particular expertise in patent law. *Cf. aaiPharma Inc. v. Thompson*, 296 F.3d 227, 241 (4th Cir. 2002). Moreover, new drug applications must include certain safety and efficacy information, including an exhaustive list of "technical sections," but none of these requirements reference patents at all. *See* 21 C.F.R. § 314.50(d). And finally, the Arava application did not even include the patents that Sandoz suggests should have informed the FDA's review.

In effect, Sandoz asks this court to modify the FDA's Arava approval from 1998 to include teriflunomide as an *additional* active ingredient based on patent applications outside the record, despite the fact that Arava's application, clinical trials, approval, and labeling all considered leflunomide as the only active ingredient. We decline Sandoz's invitation to rewrite the FDA's drug approval decision decades after the fact. On the record before it, the FDA properly examined leflunomide as the active ingredient in Arava and considered teriflunomide only as an impurity. New chemical entity exclusivity was therefore appropriate for Aubagio, which was the first drug to use teriflunomide as an active ingredient.

* * *

Consistent with the statutory and regulatory requirements for new drug approval, the FDA's approval of a new drug includes approval of the drug's active ingredient, but not its impurities. When the FDA approved Arava, it recognized teriflunomide as an impurity and hence did not approve it within the meaning of the FDCA. Teriflunomide was approved

for the first time as the active ingredient in Aubagio, which properly received new chemical entity exclusivity. Because Sandoz's challenge fails, its generic equivalent will not benefit from a period of sole marketing exclusivity. The judgment of the district court is affirmed.

So ordered.