United States Court of Appeals

FOR THE DISTRICT OF COLUMBIA CIRCUIT

Argued December 12, 2016 Decided August 29, 2017

No. 16-5229

OTSUKA PHARMACEUTICAL CO., LTD., ET AL.,
APPELLANTS

v.

THOMAS PRICE, SECRETARY, U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES, ET AL.,
APPELLEES

Appeal from the United States District Court
for the District of Columbia
(No. 1:15-cv-01688)

Thomas G. Saunders argued the cause for appellants. With him on the briefs were *Seth P. Waxman* and *Robbie Manhas*.

Henry C. Whitaker, Attorney, U.S. Department of Justice, argued the cause for federal appellees. With him on the brief were *Benjamin C. Mizer*, Principal Deputy Assistant Attorney General, and *Scott R. McIntosh*, Attorney.

William M. Jay argued the cause for intervenors-appellees Alkermes, Inc., et al. With him on the brief were *Brian T. Burgess*, *Andrew Kim*, *Sarah K. Frederick*, and *Christopher T. Holding*.

Before: BROWN and SRINIVASAN, *Circuit Judges*, and WILLIAMS, *Senior Circuit Judge*.

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

SRINIVASAN, *Circuit Judge*: The Food, Drug, and Cosmetic Act affords periods of "marketing exclusivity" to pioneering drug products. When a drug earns a period of exclusivity, the Food and Drug Administration must withhold approval of certain competing drugs if various conditions are satisfied. But how does the FDA determine if a new drug bears a sufficiently close relationship to a pioneering drug to fall within the latter's zone of exclusivity? This case concerns the FDA's test for making that determination.

The two drugs at issue in this case are antipsychotics primarily used to treat schizophrenia and bipolar disorder. The first drug, manufactured by Otsuka Pharmaceutical, is called Abilify Maintena. The second, made by Alkermes, is named Aristada.

When Alkermes sought FDA approval for Aristada, Otsuka opposed the application on the ground that Aristada's approval would violate an ongoing period of marketing exclusivity enjoyed by Abilify Maintena. Otsuka emphasized that both drugs ultimately metabolize in the body into the same molecule, and that Alkermes's application for Aristada relied in part on studies showing the safety and efficacy of a precursor product to Abilify Maintena. Otsuka argued that, in light of the relationship between the two drugs, approving Aristada would infringe on Abilify Maintena's exclusivity.

The FDA rejected Otsuka's arguments and granted approval to Aristada. The agency relied on the fact that the two products have different "active moieties"—roughly,

active ingredients. A drug's active moiety has long played a key role in determining its eligibility to receive marketing exclusivity: to be entitled to exclusivity, a drug must either contain a previously unapproved active moiety or use an approved moiety in a new way. In approving Aristada, the FDA staked out the position that a drug's active moiety not only determines its eligibility for marketing exclusivity, but also defines the field of drugs subject to that exclusivity.

Otsuka sought judicial review, contending, among other things, that the agency's same-moiety limitation on the scope of a drug's marketing exclusivity conflicts with the FDCA. The district court granted summary judgment in favor of the FDA and Alkermes. The court concluded that the FDA's same-moiety test is a reasonable construction of the statute and is consistent with the agency's regulations. We agree with the district court and affirm its decision.

I.

A.

Before a company can make a drug available for public consumption, the FDA must approve a new drug application certifying the drug's safety and efficacy. 21 U.S.C. § 355(a), (b). Until 1984, all such applications were standalone applications: applications for which the drug's proponent either conducted, or secured a right to reference, all the investigations used to demonstrate the drug's safety and efficacy. *See id*. § 355(b)(1). As a result, a company seeking approval of a new drug would regularly need to reestablish the safety and efficacy of chemical compounds used in previously approved drugs.

In order to reduce the need to conduct duplicative studies, the Drug Price Competition and Patent Term Restoration Act of 1984—better known as the Hatch-Waxman Amendments—amended the FDCA to establish two streamlined pathways to FDA approval. *See* H.R. Rep. No. 98-857, pt. 1, at 16-17 (1984). The first abbreviated route, known as an Abbreviated New Drug Application (ANDA), permits approval of "bioequivalent" (e.g., generic) versions of previously approved drugs without an independent showing of their safety and efficacy. 21 U.S.C. § 355(j)(2)(A).

The second abbreviated route, directly at issue here, enables new drug applications for non-generic drug products to rely, in part or in whole, on studies that "were not conducted by or for the applicant and for which the applicant has not obtained a right of reference" to show the applied-for drug's safety and efficacy. *Id.* § 355(b)(2). That route, known as a "(b)(2) application" due to the statutory subsection establishing it, requires an applicant to show the propriety of relying on the preexisting studies to demonstrate the applied-for drug's safety and efficacy. A (b)(2) application must also certify that sales of the applied-for drug would not infringe upon active, valid patents for any previously approved drugs invoked in support of the application. *Id.* § 355(b)(2)(A).

The Hatch-Waxman Amendments' abbreviated pathways in theory could enable competitors to "free ride" off of the work of innovators without having to foot the substantial expenses associated with safety-and-efficacy testing. As a result, the Amendments also introduced a regime of marketing exclusivity into the FDCA.

Under that system, the statute grants a first-in-time innovator a period of exclusivity during which the FDA must

deny approval of second-in-time abbreviated applications (both ANDAs and (b)(2) applications) for drug products meeting certain conditions. If an applicant seeking to use an abbreviated pathway is blocked by a previously approved drug's exclusivity, the applicant can either wait for the exclusivity period to expire, or instead submit a standalone, *non*-abbreviated application that does not rely on any previously approved drugs.

The FDCA confers marketing exclusivity under three distinct provisions, the full text of which are set out in an appendix to this opinion. We will adhere to the parties' convention by referring to the three provisions as "romanette ii," "romanette iii," and "romanette iv." 21 U.S.C. § 355(c)(3)(E)(ii)-(iv).

Romanette ii, the FDCA's broadest grant of marketing exclusivity, applies to what FDA regulations refer to as "New Chemical Entities": drugs for which "no active ingredient (including any ester or salt of the active ingredient) . . . has been approved in any other application." 21 U.S.C. § 355(c)(3)(E)(ii); 21 C.F.R. § 314.108(a). The statutory reference to a drug's "active ingredient" captures the drug's active moiety, which the regulations define as "the molecule or ion . . . responsible for the physiological or pharmacological action of the drug substance." 21 C.F.R. § 314.3(b).

Romanette ii confers an exclusivity period of five years, during which "no [abbreviated] application which refers to the [first-in-time] drug" may be approved. 21 U.S.C. § 355(c)(3)(E)(ii). FDA regulations interpret exclusivity under romanette ii to block any abbreviated application for a drug whose active moiety is the same as the New Chemical Entity. 21 C.F.R. § 314.108(a).

Romanettes iii and iv award marketing exclusivity to innovations more modest than the introduction of a New Chemical Entity. The exclusivity conferred by those provisions correspondingly is more confined in scope and duration than the five-year exclusivity afforded under romanette ii.

Under romanette iii, an application "for a drug, which includes an [active moiety] that has been approved in another application," is entitled to three years of exclusivity "if such application contains reports of new clinical investigations . . . essential to the approval of the application and conducted or sponsored by the applicant." 21 U.S.C. § 355(c)(3)(E)(iii). In other words, romanette iii confers exclusivity when a pharmaceutical company obtains approval to market a previously approved active moiety in a new formulation or for new purposes, and doing so requires it to furnish new clinical investigations to the FDA. With regard to the scope of drugs affected by the three-year exclusivity period, the FDA may not approve an abbreviated application for the same "conditions of approval of such drug in the [first-in-time] application." *Id*.

Romanette iv similarly grants a three-year exclusivity period to applicants that "supplement" a previously approved application if obtaining approval of the supplement requires submitting additional reports and investigations to the agency. *Id.* § 355(c)(3)(E)(iv). Romanette iv thus applies, for instance, to companies seeking to indicate an existing drug product for additional illnesses or otherwise alter the product's labeling. The scope of exclusivity encompasses abbreviated applications "for a change approved in the supplement" to the first-in-time drug's application. *Id*. As with the scope-delimiting phrase "conditions of approval of such drug" in romanette iii, the FDCA does not define the

precise meaning of the scope-delimiting phrase "for a change approved in the supplement" in romanette iv.

B.

In 2002, Otsuka obtained FDA approval for Abilify Tablets, an antipsychotic drug. In the ensuing fifteen years, Otsuka has received FDA approval for a number of additional drug products sharing Abilify Tablets' active moiety: aripiprazole. The formulation of aripiprazole at issue in this case, Abilify Maintena, is taken on a monthly basis by injection.

Abilify Tablets earned a five-year exclusivity period under romanette ii for introducing aripiprazole as a New Chemical Entity. Although the five-year period for Abilify Tablets lapsed nearly a decade ago, Abilify Maintena subsequently received two successive marketing-exclusivity periods of three years each. The first three-year period, which expired on February 28, 2016, came under romanette iii in connection with Abilify Maintena's initial approval. The second three-year period remains ongoing—it expires on December 5, 2017—and was awarded under romanette iv in connection with a supplemental application filed by Otsuka. That supplement involved a new study showing Abilify Maintena's efficacy in the treatment of adult schizophrenia patients experiencing an acute relapse.

On August 22, 2014, Alkermes submitted an abbreviated (b)(2) application for Aristada, another injectable antipsychotic. The application for Aristada included a clinical trial conducted by Alkermes to demonstrate the drug's safety and efficacy at intervals up to six weeks. The company also sought to rely on prior studies conducted by Otsuka demonstrating the safety and efficacy of Abilify Tablets.

Aristada shares certain chemical similarities with the Abilify line of products: Aristada's active moiety, N-hydroxymethyl aripiprazole, is a "prodrug" of aripiprazole, meaning that it ultimately metabolizes into aripiprazole in the body.

Nonetheless, under the FDA's approach to determining a drug's active moiety, which this Court upheld in *Actavis Elizabeth LLC v. FDA*, 625 F.3d 760, 765-66 (D.C. Cir. 2010), Aristada's and Abilify Maintena's active moieties are distinct. The FDA "starts with the molecule that comprises that active ingredient in the drug product, and excludes the ester and salt-bonded portions of the molecule." J.A. 426. The remaining molecule or ion is the drug's active moiety. *Id*. N-hydroxymethyl aripiprazole (Aristada) differs from aripiprazole (Abilify Maintena) in containing the "addition of a hydroxymethyl group, connected by a [non-ester] covalent C-N bond." J.A. 435. That difference suffices under the FDA's standard to distinguish the two moieties.

Otsuka filed two citizen petitions requesting that the FDA deny approval of Aristada, or, alternatively, defer its approval until Abilify Maintena's exclusivity periods lapsed. The FDA denied both petitions. The agency determined that Alkermes had properly invoked known information about aripiprazole for the purpose of demonstrating Aristada's safety and efficacy. But the agency concluded that Abilify Maintena's marketing exclusivity did not foreclose Aristada's approval because the two drugs have different active moieties. In reaching that conclusion, the FDA reasoned that the FDCA's marketing-exclusivity provisions block approval only of drug products with the same active moiety as the drug benefitting from exclusivity.

Otsuka sought review in the district court. Otsuka argued that the FDA's same-moiety requirement: (i) conflicts with

the FDCA; (ii) diverges from the agency's own regulations; and (iii) came into existence in violation of the Administrative Procedure Act because the agency effectively amended its regulations without resort to notice-and-comment procedures. Alkermes, seeking to preserve the agency's approval of Aristada, intervened in the dispute.

The district court granted summary judgment in favor of the FDA and Alkermes. *Otsuka Pharm. Co. v. Burwell*, Civ. No. 15-cv-1688, 2016 WL 4098740 (D.D.C. July 28, 2016). The court held that "the FDCA does not unambiguously prevent the FDA from determining that the FDCA's three-year exclusivity bar blocks only subsequent applications for drugs with the same active moiety," and that "it was not unreasonable for the FDA to have employed that interpretation." *Id.* at *2. The court further concluded that, because Abilify Maintena's initial exclusivity period conferred by romanette iii had expired in February 2016, Otsuka's claim under that period had become moot. *Id.* at *6 n.8. Finally, the court held that the FDA need not have undertaken notice-and-comment procedures because the same-moiety requirement was consistent with the agency's existing regulations. *Id.* at *21.

II.

The FDA understands a drug's marketing exclusivity to require withholding approval only of drug products that share the same active moiety. Otsuka challenges the agency's same-moiety interpretation, arguing that the FDCA calls for a broader understanding of the zone of marketing exclusivity conferred by romanettes iii and iv. In Otsuka's view, the FDA's interpretation cannot be squared with the statute and conflicts with the agency's own regulations. We reject

Otsuka's arguments under both the statute and the regulations, and we therefore sustain the FDA's interpretation.

At the outset, we note that Abilify Maintena's initial three-year period of exclusivity, conferred under romanette iii, has expired. As a result, we agree with the district court that Otsuka's claims with regard to that exclusivity period have become moot. *See Otsuka*, 2016 WL 4098740, at *6 n.8. But we further agree with the district court that the mootness of Otsuka's challenge concerning romanette iii does not materially affect our analysis. *See id.* Abilify Maintena's subsequent three-year exclusivity period, conferred under romanette iv, remains ongoing. And Otsuka's arguments concerning the scope of exclusivity granted by romanette iv depend on, and substantially overlap with, its arguments concerning romanette iii. As a result, understanding and addressing the former necessarily requires examining the latter.

A.

Romanettes iii and iv, in conferring a three-year period of marketing exclusivity, are ambiguous as to the relationship, if any, a second-in-time drug must bear to a first-in-time drug in order to be subject to the latter's exclusivity. All parties agree that the first- and second-in-time drugs must bear *some* relationship to one another. But they disagree about the nature of the necessary relationship. In the FDA's view, marketing exclusivity applies as between two drugs sharing the same active moiety. Otsuka, by contrast, contends that exclusivity more broadly covers any two drugs that are "legal equivalents"—a term of Otsuka's invention that draws an equivalence between two drugs whenever one relies upon the other to receive approval.

We must sustain the FDA's interpretation of the scope of exclusivity afforded by romanettes iii and iv as long as it is consistent with the statutory terms and is reasonable. *See Chevron, U.S.A., Inc. v. Nat. Res. Def. Council, Inc.*, 467 U.S. 837 (1984). The agency's understanding comfortably meets those standards.

1.

a. The FDA's basic understanding is that the extent of marketing exclusivity conferred by each of the statutory romanettes is commensurate with the degree of innovation required to earn exclusivity under it. With regard to romanette ii, therefore, the first drug to receive FDA approval for a given active moiety will block approval of all abbreviated applications for a drug with that same active moiety for five years. The scope of exclusivity under romanettes iii and iv is more limited, but so is the innovation giving rise to it.

Under romanette iii, an applicant who establishes the safety and efficacy of a previously approved active moiety for new "conditions of approval," 21 U.S.C. § 355(c)(3)(E)(iii), will thereby trigger a three-year period in which the agency must withhold approval of drugs with the same conditions of approval and the same active moiety. A parallel approach governs romanette iv, which applies when the FDA approves a "change . . . in the supplement" to a previously approved application. *Id.* § 355(c)(3)(E)(iv). In that event, a drug product seeking to make use of the "change approved in the supplement," *id.*, cannot gain approval for a period of three years if it has the same active moiety as the previously approved drug.

The upshot is that, if a pharmaceutical company innovates with respect to a given active moiety, the statutory romanettes protect the full extent of the innovation, but only against drugs with the same active moiety. A drug's active moiety thus determines its eligibility for exclusivity *and* delimits the scope of drugs whose approval is potentially foreclosed by that exclusivity.

b. Romanettes iii and iv do not specify what relationship, if any, must exist between two drugs for marketing exclusivity to come into play. But the statute contains a textual grounding for the FDA's same-moiety interpretation.

Romanette iii, in pertinent part, bars abbreviated applications "for the conditions of approval of such drug in the approved subsection (b) application." 21 U.S.C. § 355(c)(3)(E)(iii). The phrase "drug in the approved subsection (b) application" refers to "a drug, which includes an [active moiety] that has been approved in another application." *Id.* All parties correctly understand that cross-reference to refer to the first-in-time drug benefitting from exclusivity.

The statutory language, however, does not specify whether exclusivity applies whenever the second-in-time application is for the "conditions of approval" of the first-in-time drug, or whether the second-in-time application, to be excluded, must also involve the same drug as the first-in-time one. In other words, is it enough for a second-in-time application to share "*the conditions of approval* of such drug in the [first-in-time] application," or must it also be for the same "*drug* in the [first-in-time] application"? *Id.* (emphases added).

The former understanding would cast an exclusivity-bearing drug's "conditions of approval" as the sole gatekeeper of exclusivity under romanette iii, giving the scope of exclusivity a capacious reach. For instance, imagine that a company originally received approval to market a drug with a given active moiety as a means of treating depression. Then, suppose the company conducts studies showing that the drug's active moiety also addresses insomnia, and obtains approval to market a new drug product with that active moiety as an anti-insomnia medication. The new drug product would benefit from a three-year exclusivity period for that new "condition of approval" (i.e., as a treatment for insomnia). If an exclusivity-bearing drug's conditions of approval were the sole gatekeeper of exclusivity, the FDA, for three years, would be required to withhold approval of *any* drug seeking abbreviated approval to treat insomnia, regardless of whether the applied-for drug bore any chemical association with the first-in-time drug.

Unsurprisingly, the FDA rejects that interpretation. The agency instead takes the position that, in order to be subject to a first-in-time drug's exclusivity, a second-in-time application must also be for the same drug in the first-in-time application. So in the example just referenced, the first-in-time drug's exclusivity would not block all anti-insomnia treatments, regardless of chemical makeup. Rather, in keeping with the scope of the innovation giving rise to the three-year period of exclusivity, it would block only those anti-insomnia treatments involving the same drug.

That conclusion then raises a second ambiguity: when should a second-in-time drug be considered the same as the drug in the first-in-time application? The agency rejects a narrow understanding under which "exclusivity covers only specific drug products and therefore protects from generic

competition only the first approved version of a drug, or change in a drug." *Abbreviated New Drug Application Regulations*, 54 Fed. Reg. 28,872-01, at 28,897 (July 10, 1989). Construing the statute in that way would provide little protection to innovators. For instance, a second-in-time (b)(2) applicant could easily move itself outside a previously approved drug product's zone of exclusivity merely by altering one of that product's *inactive* ingredients.

The FDA instead concludes that a first-in-time drug's marketing exclusivity attaches, not to the specific drug product receiving approval, but to a particular feature of the drug: its active moiety. The agency derives that understanding from the fact that all three romanettes condition a drug's eligibility for exclusivity on whether its "active ingredient (including any ester or salt of the active ingredient)"—i.e., its active moiety—has been approved in a previous application. 21 U.S.C. § 355(c)(3)(E)(ii)-(iv). Noting that romanette iii's language, "such drug in the [first-in-time] application," refers to "a drug, which includes an [active moiety] that has been approved in another application," the FDA concludes that any second-in-time drug that includes an exclusivity-benefitted drug's active moiety is likewise subject to its exclusivity. Having long considered a drug's active moiety to be its distinguishing feature for purposes of determining its eligibility for marketing exclusivity, *see Abbreviated New Drug Application Regulations; Patent and Exclusivity Provisions*, 59 Fed. Reg. 50338-01, at 50357-58 (Oct. 3, 1994), the FDA here correspondingly concludes that marketing exclusivity under romanette iii does not apply to a second-in-time drug with "conditions of approval" that may overlap with those of the first-in-time drug, but with a *different* active moiety.

The FDA interprets romanette iv in parallel fashion. Under that provision, an abbreviated application will be barred during a first-in-time drug's three-year exclusivity period if it is "for a change approved in the supplement" to the previously approved application. 21 U.S.C. § 355(c)(3)(E)(iv). The statutory language, again, does not specify whether, to be excluded, it is enough for a second-in-time abbreviated application to be "*for a change* approved in the supplement" to the first-in-time application, or whether it must also be *for the drug* in the supplemented application.

Mirroring its treatment of romanette iii, the FDA opted for the latter interpretation. The agency begins by noting that a pharmaceutical company cannot alter the active moiety of a drug product when supplementing the drug's application. *See Guidance for Industry: Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees*, FOOD & DRUG ADMIN. 3 (Dec. 2004). As a result, "a change approved in the supplement" to an application must be a change in the conditions of approval for *that* specific drug—for instance, an alteration in its labeling or indications, as with Abilify Maintena's supplemented labeling indicating its efficacy in treating adult schizophrenia patients experiencing an acute relapse.

The FDA correspondingly reads romanette iv to provide that, to infringe a previously approved drug's three-year exclusivity under that provision, a second-in-time application must not only be for the "change approved in the supplement" to the previously approved drug's application, but also must be for the same drug (i.e., a drug containing the same active moiety). Marketing exclusivity therefore would not apply, for instance, to an abbreviated application for a drug with a different active moiety, the label for which happened to

overlap in some way with the first-in-time drug's supplemented labeling.

2.

Otsuka contends that the FDA's same-moiety limitation on the scope of exclusivity conferred by romanettes iii and iv is inconsistent with the statute. Because none of Otsuka's arguments "unambiguously foreclose[s] the agency's construction of the statute," we defer to the FDA's reasonable interpretation. *Cablevision Sys. Corp. v. FCC*, 649 F.3d 695, 704 (D.C. Cir. 2011); *accord Actavis*, 625 F.3d at 765.

a. Otsuka's central submission is that a principle it terms "legal equivalence" must be read into the FDCA's marketing-exclusivity provisions. Legal equivalence, as Otsuka conceives it, is broader than (but apparently inclusive of) equivalence in active moieties. And if two drugs are legally equivalent, Otsuka posits, approval of the second-in-time drug should be subject to the first-in-time drug's exclusivity, regardless of whether the two drugs share the same active moiety.

Otsuka appears to believe that two drugs should be considered legal equivalents in at least the following scenarios: (i) the two drugs share the same active moiety; (ii) one drug relies on the other drug to receive FDA approval; or (iii) one drug relies on a drug that is itself legally equivalent to (i.e., satisfies one of the first two conditions with respect to) the other drug. On that understanding, Aristada and Abilify Maintena are legally equivalent: Aristada relied in its application on Abilify Tablets, which in turn is legally equivalent to Abilify Maintena because the two drugs share the same active moiety (aripiprazole), and also because Abilify Maintena itself relied on Abilify Tablets for approval.

Consequently, as Otsuka sees it, the FDA erred by permitting Aristada to rely on aripiprazole (Abilify Tablets) for approval, but treating Aristada as distinct from aripiprazole (Abilify Maintena) for purposes of defining the latter product's zone of exclusivity.

Congress perhaps could have written a statute under which, if one drug relies on the safety or efficacy of a previously approved drug to obtain approval, the two drugs must be considered "legally equivalent" for purposes of defining the previously approved drug's zone of exclusivity. But the statutory romanettes nowhere expressly set out any concept of legal equivalence in describing the scope of marketing exclusivity. Instead, Otsuka claims to find a footing for its theory in the FDCA's provisions governing new drug applications, which in turn, the company contends, informs the proper interpretation of the romanettes.

Otsuka's complex, multi-layered theory begins with the FDCA's condition that a new drug application must contain "full reports of investigations which have been *made to show* whether or not such drug is safe for use and whether such drug is effective in use." 21 U.S.C. § 355(b)(1) (emphasis added). Otsuka notes that an abbreviated (b)(2) application, which must also satisfy that condition, can do so by relying on studies showing the safety and efficacy of an already approved drug. As a result, Otsuka reasons, at least some of the investigations submitted in connection with a (b)(2) application would "have been *made* to show," not that the *applied-for* drug is safe and effective, but that the *relied-upon* drug is safe and effective.

With that premise in mind, Otsuka returns to § 355(b)(1)'s statement that a new drug application (including a (b)(2) application) must contain "full reports of

investigations which have been made to show whether or not *such drug*" is safe and effective. *Id.* (emphasis added). Because at least some of the investigations invoked in support of a (b)(2) application will concern the relied-upon drug, Otsuka reasons, the phrase "such drug" in § 355(b)(1) must encompass, not just the drug for which approval is sought, but also any drug on which the application relies. In that way, Otsuka submits, the phrase "such drug" necessarily embraces a concept of legally equivalent drugs—i.e., drugs treated as the same drug under the statute because one relied on the other to secure approval.

Otsuka's theory cannot stop there, because the company still needs to export the concept of legal equivalence from § 355(b)(1), which pertains to new drug applications, into the statutory romanettes, which pertain to marketing exclusivity. For that next step, Otsuka invokes the general assumption that "identical words used in different parts of the same act are intended to have the same meaning." *Comm'r v. Lundy*, 516 U.S. 235, 250 (1996) (quoting *Sullivan v. Stroop*, 496 U.S. 478, 484 (1990)). That assumption means, to Otsuka, that the phrase "such drug" must embrace a drug and its legal equivalents, not just in § 355(b)(1), but anywhere that phrase appears in the pertinent provisions of the FDCA.

One such provision is romanette iii. In relevant part, romanette iii blocks approval of second-in-time (b)(2) applications "for the conditions of approval of *such drug*" in the first-in-time application. 21 U.S.C. § 355(c)(3)(E)(iii) (emphasis added). Otsuka reasons that, because "such drug" in § 355(b)(1) refers to a drug and its legal equivalents, "such drug" in romanette iii likewise should embrace a drug's legal equivalents. As a result, Otsuka concludes, the marketing exclusivity afforded by romanette iii requires withholding

approval of any drugs that are legally equivalent to the first-in-time drug and share its conditions of approval.

Finally, although romanette iv (as opposed to romanette iii) does not contain the words "such drug," Otsuka suggests that the concept of legal equivalence should be read into romanette iv, as well, in order to maintain symmetry across the romanettes with regard to the scope of marketing exclusivity. The endpoint of Otsuka's multi-step interpretation thus is that a second-in-time drug is subject to the marketing exclusivity of any drug it relies upon (and that drug's legal equivalents), regardless of whether the drugs share the same active moiety.

b. For Otsuka's theory to prevail, it would need to show not only that its interpretation is permissible, but that the agency's alternative understanding is not. *See, e.g.*, *Actavis*, 625 F.3d at 765. Otsuka falls far short of making that showing.

To start with the initial premise of Otsuka's theory, the FDA's competing reading of § 355(b)(1)'s "made to show"/"such drug" language is entirely reasonable. Otsuka's interpretation, as explained, construes the phrase "such drug" to refer simultaneously to the applied-for drug (e.g., Aristada) and any drug on which the application relies (e.g., Abilify Tablets)—which, to Otsuka, means that "such drug" embodies a concept of legal equivalence between the applied-for drug and any relied-upon drug. The agency, by contrast, interprets "such drug" to refer solely to the applied-for drug.

The agency's interpretation draws significant support from the statutory history. For nearly a half century, "such drug" could have referred only to the applied-for drug. Those words were part of the original FDCA in 1938, in the

precursor provision to § 355(b). *See* Food, Drug, and Cosmetic Act, Pub. L. No. 75-717, § 505(b), 52 Stat. 1040, 1052 (1938). And it was not until the Hatch-Waxman Amendments in 1984 that the statute even provided for abbreviated pathways through which an applicant could rely on investigations concerning a previously approved drug. Until then, consequently, the "investigations which have been made to show whether or not such drug" is safe and effective necessarily referred to investigations showing the safety and efficacy of the applied-for drug, not any previously approved drug.

To the extent those same words could have taken on a new meaning following introduction of the abbreviated pathways in 1984, the agency's interpretation of "such drug" to mean (only) the applied-for drug remains entirely sound. Under that interpretation, an application can satisfy § 355(b)(1)'s condition—that it include "full reports of investigations which have been made to show whether or not such drug is safe and effective for use"—as long as the investigations show the *applied-for drug*'s safety and effectiveness. To be sure, in a (b)(2) application, the investigations relied upon can include ones that originally involved testing of a previously approved drug. But those investigations still could serve to show—and thus could qualify as now being "made to show"—the applied-for drug's safety and effectiveness, provided the drug's proponent established a scientific basis for reaching that conclusion.

In that light, the agency's reading of "made to show"/"such drug" in § 355(b)(1) is fully reasonable, and considerably more straightforward than Otsuka's. And because the agency understands "such drug" to refer solely to the applied-for drug, its reading, unlike Otsuka's, does not

involve any concept of legal equivalence between an applied-for drug and other drugs on which it may rely.

Even if we assume Otsuka's reading of "such drug" in § 355(b)(1) is controlling, Otsuka again falls short in its effort to transport its preferred understanding of "such drug" from § 355(b)(1) into the statutory romanettes. Because Otsuka cannot make that essential showing, its statutory argument, independent of any other shortcomings, must fail.

Otsuka asserts that we should treat the words "such drug," which appear nearly fifty times in Section 505 of the FDCA alone, as a statutory term of art. Doing so would be the *reductio ad absurdum* of the "normal rule of statutory construction that identical words used in different parts of the same act are intended to have the same meaning." *Lundy*, 516 U.S. at 250 (citation omitted). By nature, the object of the word "such" entirely depends on context. *See Such*, MERRIAM-WEBSTER'S COLLEGIATE DICTIONARY (11th ed. 2003) (defining "such" as "of the character, quality, or extent previously indicated or implied"). Consequently, the words "such drug" might readily refer to one drug in one instance and another drug in another.

So even if it were true—which it is not—that the words "such drug" in § 355(b)(1) can only be read to refer simultaneously to the applied-for *and* the relied-upon drug, it would not necessarily follow that those words in romanette iii should carry the same meaning. Whereas § 355(b)(1) pertains to new drug applications, romanette iii is a distinct provision dealing with the distinct subject of marketing exclusivity. As a result, even if § 355(b)(1)'s reference to "such drug" encompasses drugs that rely on one another for purposes of meeting the criteria for a new drug application, that still would not establish that the same, legal-equivalence

understanding must inform a separate provision dealing with a separate subject.

Once again, the agency's competing interpretation of the relevant statutory language is entirely reasonable. The agency reads the language of romanette iii to indicate that "such drug," in context, refers only to the first-in-time drug benefitting from exclusivity. The provision precludes the FDA from approving an ANDA or (b)(2) application "for the conditions of approval of *such drug in the approved subsection (b) application*," which in turn refers to the drug that "includes an [active moiety] that has been approved in another application." 21 U.S.C. § 355(c)(E)(iii) (emphasis added). "Such drug," then, is a specific "approved" drug: namely, the drug (i.e., active moiety) entitled to the three-year period of exclusivity conferred by romanette iii. Nothing in the statute requires concluding that the reference to "such drug" automatically embraces so-called legal equivalents to it. (And that is to say nothing of the fact that romanette iv, unlike romanette iii, does not contain the words "such drug" at all.)

The implications of Otsuka's conception of legal equivalence further counsel against concluding that Congress intended to incorporate it into the statutory romanettes. Under Otsuka's interpretation, if one drug relies on another to obtain abbreviated approval for the same conditions of approval, the relied-upon drug's zone of exclusivity necessarily encompasses the applied-for drug. That theory would apply regardless of the reason that the abbreviated application relied on the previously approved drug.

But a (b)(2) application can rely on *any* scientific investigations, including general academic literature, that help to establish the applied-for drug's safety and efficacy. *See id.* § 355(b)(1). So, for instance, a (b)(2) application could

rely—and in at least one instance has relied, Intervenor Br. 30-31 & n.10—on a prior study to show the safety of an *inactive* ingredient in the applied-for drug. Otsuka's reading thus would treat two drug products as legally equivalent, such that one's exclusivity would preclude approval of the other, even though the only intersection between the two products involved an *inactive* ingredient. There is no reason to suppose Congress intended the scope of a drug's marketing exclusivity to sweep so far.

Otsuka's notion of legal equivalence also stands in considerable tension with our decision in *Actavis Elizabeth LLC v. FDA*, 625 F.3d 760 (D.C. Cir. 2010). That case involved prodrugs (which, as noted, are drugs that eventually metabolize into a different chemical compound in the body). We upheld the FDA's understanding that a prodrug of a previously approved drug, if it has a different active moiety, can qualify as a "major innovation[]" entitled to "'[N]ew [C]hemical [E]ntity' status and the resulting five-year exclusivity" afforded under romanette ii. *Id.* at 765. We said we would be "hard pressed to second guess" the FDA's considered view that such a drug is sufficiently "distinct" so as to be "uniquely deserving" of New Chemical Entity status. *Id.* at 765-66.

If we accepted Otsuka's assertion that the scope of marketing exclusivity under the FDCA is governed by a principle of legal equivalence, that principle would apply no less to the five-year exclusivity period granted by romanette ii than to the three-year periods granted by romanettes iii and iv. According to Otsuka's reading, consequently, the FDA would be required to treat a New Chemical Entity entitled to a five-year exclusivity period under *Actavis*—i.e., a "major innovation" containing no active moiety that "has been approved in any other application," 21 U.S.C.

§ 355(c)(3)(E)(ii)—as equivalent to any previously approved drug on which it relied for approval. Otsuka fails to persuade us that the FDCA unambiguously contains a principle of legal equivalence under which even a drug earning the status of a *New* Chemical Entity is equivalent to a previously approved drug.

c. Otsuka does not advance its cause by relying on the patent-certification measures pertaining to (b)(2) applications. A (b)(2) applicant must certify that sale of the applied-for drug would not infringe upon a valid patent with respect to any relied-upon drug. *See* 21 U.S.C. § 355(b)(2)(A). The provision states that the applicant must include a certification "with respect to each patent which claims the drug for which such investigations were conducted or which claims a use for *such drug* for which the applicant is seeking approval." *Id.* (emphasis added). Otsuka's argument with regard to that language parallels its earlier argument under § 355(b)(1). Otsuka again asserts that "such drug" in the patent-certification provision refers both to the relied-upon and the applied-for drug, and that the words thus embody a principle of legal equivalence. Otsuka accordingly claims that the FDA "effectively conced[ed]" that Aristada and Abilify Maintena are legally equivalent when it required Alkermes' new drug application for Aristada to certify to method-of-use patents for aripiprazole. Appellants' Br. 28.

Otsuka gets no further with this legal-equivalence argument than it did with the earlier one. Here, too, Otsuka's reading of "such drug" is hardly compelled. Those words refer back to "the drug for which [the relied-upon] investigations were conducted." 21 U.S.C. § 355(b)(2)(A). That drug is the relied-upon drug, not the applied-for drug. And although the words "such drug" appear in a phrase referring to a patent "which claims a use for such drug *for*

which the applicant is seeking approval," *id.* (emphasis added), the emphasized language is most naturally read to modify "use," not "such drug"—i.e., the "*use* . . . for which the applicant is seeking approval," not the "*drug* for which the applicant is seeking approval." So understood, "such drug" refers solely to the relied-upon drug, not to both the relied-upon and applied-for drugs.

In any event, even if we assume Otsuka's understanding of "such drug" in the patent-certification provision is controlling, Otsuka once again runs aground in assuming that its preferred interpretation of "such drug" in that provision would necessarily carry over to "such drug" in romanette iii. The patent-certification provision is a prophylactic measure to notify a patent holder of *possible* infringement by a new drug application that relies on one of its drugs. In that light, the fact that Alkermes was required to certify to Otsuka's method-of-use patents for aripiprazole in no way constitutes a concession that the two drugs are "equivalent" for purposes of the FDCA's marketing-exclusivity provisions. As the agency has explained, marketing exclusivity under the romanettes is a distinct form of protection from that afforded by the patent system. *See generally Frequently Asked Questions on Patents and Exclusivity*, FOOD & DRUG ADMIN., https://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm079031.htm (last updated Dec. 5, 2016). We see no reason to conclude that the patent-certification provision does anything more than guard against patent infringement, without speaking to—much less defining—the zone of a drug's marketing exclusivity.

d. In a final attempt to persuade the Court, Otsuka warns of the practical implications of upholding the FDA's same-moiety requirement. According to Otsuka, unless the scope of marketing exclusivity extends to legally equivalent drugs,

competitors will be able to rely on an innovator's drug while readily evading its exclusivity. In particular, Otsuka explains that "[p]ioneer drug companies will be reluctant to develop new, innovative drugs if their marketing exclusivity can be easily circumvented by a follow-on company that creates a prodrug of the pioneer product's active moiety." Appellants' Br. 18.

Otsuka's argument in that respect boils down to an attempt to re-litigate this Court's decision in *Actavis*, 625 F.3d 760. There, as explained, we upheld the FDA's position that a prodrug of a previously approved drug, if it contains a different active moiety, is entitled to the five-year exclusivity period granted to a New Chemical Entity. Otsuka's argument that the statute should be read to bar competitors from receiving approval for such prodrugs thus "represent[s] little more than question-begging": "In the FDA's view," prodrugs with previously unapproved active moieties "*are* 'major innovations' deserving five-year exclusivity," even if they ultimately metabolize into a previously approved active moiety. *Id.* at 765-66. We have no occasion to revisit our decision in *Actavis*, or to question the FDA's expert judgment that "even minor covalent structural changes are capable of producing . . . major changes in the activity of a drug." *Id.*

* * *

For those reasons, Otsuka fails to show that the language of the FDCA unambiguously compels its "legal-equivalence" interpretation of the scope of marketing exclusivity under the romanettes. Rather, the agency's same-moiety interpretation is reasonable and warrants our deference.

B.

As a fallback to its statutory arguments, Otsuka claims that the FDA's same-moiety interpretation should be rejected as irreconcilable with the agency's own regulations and past statements. "An agency's interpretation of its own regulations is entitled to judicial deference," and is controlling unless "plainly erroneous or inconsistent with the regulation[s]." *Actavis*, 625 F.3d at 763 (internal quotation marks omitted). We see no reason to reject the FDA's same-moiety interpretation as incompatible with the agency's regulations implementing the statutory romanettes. Those regulations largely parrot the language of the romanettes, which, as we have found, comfortably accommodate the agency's same-moiety rule. The same is true of the regulations.

Otsuka observes that the regulation implementing romanette ii explicitly imposes a "same active moiety" limitation on the scope of the five-year exclusivity period conferred by that provision. 21 C.F.R. § 314.108(b)(2). By contrast, Otsuka notes, the regulations pertaining to romanettes iii and iv contain no such language expressly establishing a same-moiety requirement. *See id.* §§ 314.108(b)(4), (b)(5). As a result, Otsuka reasons, the latter regulations should be understood implicitly to reject a same-moiety limitation. We disagree.

Under Otsuka's reading, the three-year exclusivity periods under romanettes iii and iv would be *broader* in scope—because they would be unencumbered by a same-moiety limitation—than the five-year period conferred by romanette ii. That result would make little sense. Romanette ii confers exclusivity in connection with a more significant innovation, and hence awards a longer exclusivity period,

than romanettess iii and iv. If anything, then, one would expect romanette ii to grant a broader scope of exclusivity. In that light, the agency can permissibly understand the express inclusion of a same-moiety limitation in the romanette-ii regulation to make especially clear that such a limitation constrains the broader exclusivity conferred by that regulation, rather than to imply that the same limitation does not govern the narrower exclusivity conferred by the romanette-iii and -iv regulations.

Otsuka next points to the language of the regulation corresponding to romanette iii. That regulation, Otsuka emphasizes, provides that three-year marketing exclusivity under romanette iii bars second-in-time applications "for the conditions of approval of the original application" rather than "for the conditions of approval of such drug." *Id*. § 314.108(b)(4). Otsuka argues that the absence of the "such drug" language undermines the agency's position that the regulation accommodates a same-moiety limitation. But it is Otsuka, not the FDA, that attaches dispositive significance to the words "such drug." The FDA, for its part, persuasively contends that the phrase "the conditions of approval of the original application" can just as easily accommodate a same-moiety limitation as the phrase "the conditions of approval of such drug."

Otsuka also identifies past FDA statements that it reads to be incompatible with the agency's present espousal of a same-moiety limitation. But the only instance in which the agency appears to have squarely expressed a contrary view was in a 2010 opinion letter concerning the glaucoma medicine Lumigan. In that letter, the FDA stated that Lumigan "could not [have] receive[d] approval for 3 years" following another drug's (Xalatan's) receipt of a three-year exclusivity period under romanette iii, even though the two drugs have different

active moieties. J.A. 121. The FDA's position in that letter plainly assumed that romanette iii does not include a same-moiety limitation.

Agencies, however, can change their interpretations provided that they acknowledge and explain the change and the new position is otherwise permissible. *See FCC v. Fox Television Stations, Inc.*, 556 U.S. 502, 516 (2009). That is what the FDA did in this case. In its letter denying Otsuka's petitions, the FDA explicitly acknowledged its comments in the Lumigan letter. The denial letter then explained the agency's various reasons for adopting its present position now that the issue was "squarely before the Agency." J.A. 441 n.87. Those reasons mirror the ones discussed throughout this opinion. In those circumstances, there is no reason to deny deference to the agency's present interpretation.

Finally, we are unpersuaded by Otsuka's contention that the agency was required to adopt the same-moiety limitation through notice-and-comment rulemaking. Because the same-moiety requirement is not "a new position inconsistent with an existing regulation" and does not work "a substantive change in [any] regulation," there was no need for the FDA to have undertaken notice and comment procedures before adopting it. *U.S. Telecomm. Ass'n v. FCC*, 400 F.3d 29, 35 (D.C. Cir. 2005) (emphasis and internal parenthesis removed).

* * * * *

For the foregoing reasons, we affirm the district court's grant of summary judgment.

So ordered.

Appendix

21 U.S.C. § 355(c)(3)(E)

(ii) If an application submitted under subsection (b) of this section for a drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under subsection (b) of this section, is approved after September 24, 1984, no application which refers to the drug for which the subsection (b) application was submitted and for which the investigations described in clause (A) of subsection (b)(1) of this section and relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted may be submitted under subsection (b) of this section before the expiration of five years from the date of the approval of the application under subsection (b) of this section, except that such an application may be submitted under subsection (b) of this section after the expiration of four years from the date of the approval of the subsection (b) application if it contains a certification of patent invalidity or noninfringement described in clause (iv) of subsection (b)(2)(A) of this section. The approval of such an application shall be made effective in accordance with this paragraph except that, if an action for patent infringement is commenced during the one-year period beginning forty-eight months after the date of the approval of the subsection (b) application, the thirty-month period referred to in subparagraph (C) shall be extended by such amount of time (if any) which is required for seven and one-half years to have elapsed from the date of approval of the subsection (b) application.

(iii) If an application submitted under subsection (b) of this section for a drug, which includes an active ingredient (including any ester or salt of the active ingredient) that has

been approved in another application approved under subsection (b) of this section, is approved after September 24, 1984, and if such application contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant, the Secretary may not make the approval of an application submitted under subsection (b) of this section for the conditions of approval of such drug in the approved subsection (b) application effective before the expiration of three years from the date of the approval of the application under subsection (b) of this section if the investigations described in clause (A) of subsection (b)(1) of this section and relied upon by the applicant for approval of the application were not conducted by or for the applicant and if the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted.

(iv) If a supplement to an application approved under subsection (b) of this section is approved after September 24, 1984, and the supplement contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the supplement and conducted or sponsored by the person submitting the supplement, the Secretary may not make the approval of an application submitted under subsection (b) of this section for a change approved in the supplement effective before the expiration of three years from the date of the approval of the supplement under subsection (b) of this section if the investigations described in clause (A) of subsection (b)(1) of this section and relied upon by the applicant for approval of the application were not conducted by or for the applicant and if the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted.