United States Court of Appeals

FOR THE DISTRICT OF COLUMBIA CIRCUIT

Argued September 20, 2010 Decided November 9, 2010

No. 10-5066

ACTAVIS ELIZABETH LLC,
APPELLANT

v.

UNITED STATES FOOD AND DRUG ADMINISTRATION, ET AL.,
APPELLEES

Appeal from the United States District Court
for the District of Columbia
(No. 1:09-cv-00362)

Chad A. Landmon argued the cause for appellant. With him on the briefs was *Robert B. Greenbaum*.

Andrew E. Clark, Senior Litigation Counsel, U.S. Department of Justice, argued the cause for federal appellees. With him on the brief were *Eugene M. Thirolf Jr.*, Director, and *Eric M. Blumberg*, Deputy Chief Counsel, U.S. Department of Health & Human Services. *R. Craig Lawrence*, Assistant U.S. Attorney, entered an appearance.

George F. Pappas, *Peter O. Safir*, and *Emily J. Henn* were on the brief for appellee Shire Pharmaceuticals, Inc.

Before: BROWN, *Circuit Judge*, and EDWARDS and RANDOLPH, *Senior Circuit Judges*.

Opinion for the Court filed by *Senior Circuit Judge* RANDOLPH.

RANDOLPH, *Senior Circuit Judge*: This is an appeal from the order of the district court granting summary judgment against Actavis Elizabeth LLC. In 2007, the Food and Drug Administration approved Vyvanse, a name-brand drug for the treatment of attention deficit hyperactivity disorder. Two years later, Actavis submitted an application for lisdexamfetamine dimesylate, a generic version of the same drug. The FDA returned Actavis' application. It did so because it had previously determined that Vyvanse was entitled to five years of marketing exclusivity under the Hatch-Waxman Amendments to the Federal Food, Drug, and Cosmetic Act. Actavis brought this action claiming that Vyvanse was not entitled to five years of exclusivity.

I

New drugs, including generic versions of previously approved drugs, may not be marketed without the FDA's approval. *Purepac Pharm. Co. v. Friedman*, 162 F.3d 1201, 1201 (D.C. Cir. 1998). The approval process is governed by the Federal Food, Drug, and Cosmetic Act, as amended by the Drug Price Competition and Patent Term Restoration Act of 1984 (known as the "Hatch-Waxman Amendments"), Pub. L. No. 98-417, 98 Stat. 1585. So-called "new drug applications"—required for "pioneer" drugs that have never before received FDA approval—must be supported by full reports of investigations showing the drug is safe and effective. 21 U.S.C. § 355(b)(1); *Serono Labs., Inc., v. Shalala*, 158 F.3d 1313, 1316 (D.C. Cir. 1998). The Hatch-Waxman

Amendments allowed generic versions of previously approved drugs to gain approval through the submission of an "[a]bbreviated new drug application." 21 U.S.C. § 355(j).[1] These abbreviated applications reduce the effort required to gain marketing approval by, among other things, allowing the applicant to rely on clinical studies submitted as part of a previous new drug application. *Id.* § 355(j)(2)(A)(i)-(v); *Mylan Labs., Inc. v. Thompson*, 389 F.3d 1272, 1275 (D.C. Cir. 2004).

The Hatch-Waxman Amendments also grant various periods of marketing exclusivity to certain pioneer drugs approved under § 355(b). The exclusivity provisions protect these drugs from generic competition for the specified terms by preventing the submission of abbreviated applications that refer to them. *See* 21 U.S.C. § 355(j)(5)(F)(i)-(v). At issue here, § 355(j)(5)(F)(ii) provides that

> [i]f 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 may be submitted under this subsection which refers to the drug before the expiration of five years from the date of the approval . . ..

Id. § 355(j)(5)(F)(ii).

In addition to this five-year period, the Amendments grant three-year exclusivity to drugs that include previously approved active ingredients if the application for the drug "contains

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[1] Among other requirements, generic drugs must contain the same active ingredients as a "listed drug" that has already received FDA approval. *See* 21 U.S.C. § 355(j)(2)(A)(i)-(viii).

reports of new clinical investigations . . . essential to the approval of the application and conducted or sponsored by the applicant . . .." *Id.* § 355(j)(5)(F)(iii).

The FDA has implemented these exclusivity provisions through regulations. 21 C.F.R. § 314.108. The regulations give five years of exclusivity for each "drug product that contains a new chemical entity." *Id.* § 314.108(b)(2). A "new chemical entity" is "a drug that contains no active moiety that has been approved by FDA in any other" new drug application. *Id.* § 314.108(a). "Active moiety" is defined as "the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance." *Ibid.* Thus, to qualify for five-year exclusivity under § 355(j)(5)(F)(ii), an approved drug must contain no previously approved active moieties.

In 2005, New River Pharmaceuticals, the predecessor in interest to intervenor-defendant Shire Pharmaceuticals, sought approval to market lisdexamfetamine dimesylate for the treatment of attention deficit hyperactivity disorder under the brand name Vyvanse. Vyvanse received FDA approval on February 23, 2007. The agency determined that the drug was entitled to a five-year period of exclusivity under its regulations. In January 2009, Actavis submitted its abbreviated application for the generic drug lisdexamfetamine dimesylate.[2] Its application referenced Vyvanse. The FDA returned Actavis'

[2] Because the FDA returned Actavis' abbreviated application, it never determined whether the drug qualified for approval under § 355(j). For sake of simplicity, we refer to lisdexamfetamine dimesylate as the generic version of Vyvanse.

application unfiled because Vyvanse's period of market exclusivity had not expired. *See* 21 C.F.R. § 314.101(e)(2). Actavis brought this suit in the district court under the Administrative Procedure Act, seeking to force the agency to rescind its grant of exclusivity to Vyvanse and to accept Actavis' abbreviated application. In response, the agency began its own administrative review of the matter, during which the suit was stayed. In October 2009, the FDA affirmed its original determination, and the case resumed. The district court eventually granted summary judgment to the agency and Shire on all claims.

II

A

To understand Actavis' arguments, it is necessary briefly to describe the chemical structure of lisdexamfetamine dimesylate, the drug molecule in question. Lisdexamfetamine dimesylate is a salt of lisdexamfetamine. Since, under the agency's regulations, salts are not considered active moieties, the agency's analysis centered on the lisdexamfetamine molecule alone. Lisdexamfetamine consists of a portion of lysine, a common amino acid, connected to dextroamphetamine. These two parts are linked by an amide bond, a type of covalent bond that utilizes a nitrogen atom to perform the linking function.[3]

What is important is that once it enters the body, lisdexamfetamine undergoes a chemical conversion to produce dextroamphetamine. In industry parlance, this makes

[3] Covalent bonds are formed between two atoms when those atoms share a pair of electrons. HAWLEY'S CONDENSED CHEMICAL DICTIONARY 342 (15th ed. 2007).

lisdexamfetamine a "prodrug" of dextroamphetamine.[4] HAWLEY'S CONDENSED CHEMICAL DICTIONARY 1043 (15th ed. 2007). Drugs containing dextroamphetamine, but not lisdexamfetamine, had received FDA approval before New River filed its application for Vyvanse.

B

There is little to Actavis' argument that the award of five-year exclusivity to Vyvanse conflicted with the FDA's regulations. The agency interprets its regulations to allow five-year exclusivity for drugs containing derivative molecules of previously approved "active moieties" when those derivative molecules contain non-ester covalent bonds.[5] As the FDA explained in its final decision with regard to Vyvanse: "Under FDA's interpretation of its regulation, the active moiety of a molecule with a non-ester covalent bond is the entire molecule, even if the molecule includes a covalent bond to a molecule that was itself previously an active moiety."

An agency's interpretation of its own regulations is entitled to judicial deference. *Mistick PBT v. Chao*, 440 F.3d 503, 511 (D.C. Cir. 2006). Although a court will reject an agency's interpretation when it is shown to be "plainly erroneous or inconsistent with the regulation," Actavis has not met that standard. *Thomas Jefferson Univ. v. Shalala*, 512 U.S. 504, 512 (1994); *see also Office of Commc'n, Inc. v. FCC*, 327 F.3d 1222, 1224-25 (D.C. Cir. 2003).

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[4] The parties also refer to the lisdexamfetamine molecule as a "derivative" of dextroamphetamine.

[5] An ester bond is a type of covalent bond that uses an oxygen atom to perform the linking function.

The regulatory definition of "active moiety" excludes only "those appended portions of the molecule that cause the drug to be an ester, salt . . ., or other noncovalent derivative." 21 C.F.R. § 314.108(a). When the drug molecule is not in the form of an ester, salt, or other noncovalent derivative, the FDA treats the entire molecule as that "responsible for the physiological or pharmacological action of the drug substance," and therefore a separate "active moiety." *Ibid.* Any drug that does not contain a previously approved active moiety is entitled to five-year exclusivity. *Id.* § 314.108(a), (b)(2). This leaves certain types of prodrugs eligible for five-year exclusivity—namely, those that are not esters, salts, or other types of noncovalent derivatives. The FDA's interpretation is squarely within the language of its regulations. And since lisdexamfetamine contains an amide bond, the FDA properly treated it as an "active moiety" of its own.

C

Actavis spends the bulk of its briefs arguing that the FDA's interpretation is inconsistent with the clear meaning of the statute. Where Actavis sees clarity we see ambiguity.

Under the Hatch-Waxman Amendments, five-year exclusivity is granted to drugs "no active ingredient (including any ester or salt of the active ingredient) of which" has been approved in a prior new drug application. 21 U.S.C. § 355(j)(5)(F)(ii). Actavis thinks this language prevents the FDA from granting five-year exclusivity to any drug containing a drug molecule (such as lisdexamfetamine) that eventually produces a previously approved drug molecule in the body. In addition, the company believes that the FDA's interpretation allowing such exclusivity upends the incentive scheme created by Congress and "eviscerates" the distinction between three- and five-year exclusivity.

Actavis relies mainly on the term "active ingredient," which it says obligates the FDA to identify the particular drug molecule that reaches the "site" of the drug's action. This molecule, Actavis argues, is necessarily the "active ingredient" of the drug in question, regardless of the form of the molecule before it enters the body. But there is nothing to indicate that Congress used the term in the sense Actavis urges. The Hatch-Waxman Amendments do not define active ingredient. The legislative history establishes only that Congress was concerned with providing incentives for innovation by granting five-year exclusivity to "new chemical entities" and is silent on what determines novelty. *See* 130 Cong. Rec. 24425 (1984) (statement of Rep. Waxman).[6]

The word "active," standing alone, does not get Actavis any further. Actavis argues that by using the term "active," Congress was requiring the FDA to determine the particular molecule that provides the drug's "activity," which it claims is limited to the drug's specific therapeutic effect. If this molecule has been previously approved, then five-year exclusivity is not warranted. But the FDA is right—or at least we have been given no reason to doubt—that the activity of a drug cannot be reduced to such a simple formulation. The agency has concluded that, for certain types of prodrugs, the entire pre-ingestion drug molecule should be deemed responsible for

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[6] We note that FDA has adopted different definitions of "active ingredient" in different statutory contexts. *See* 21 C.F.R. § 210.3(b)(7); 54 Fed. Reg. 28872, 28881 (July 10, 1989). None of these definitions accord with the "plain meaning" of "active ingredient" urged by Actavis. In addition, the Federal Circuit has held that "active ingredient" has a plain meaning that, if adopted, would allow more prodrugs to attain five-year exclusivity than the FDA's current interpretation. *See Photocure ASA v. Kappos*, 603 F.3d 1372, 1376 (Fed. Cir. 2010).

the drug's activity, which can include its "distribution within the body, its metabolism, its excretion, or its toxicity." There is no reason to believe Congress thought differently—or thought about it at all.

Our court has dealt with this particular language of the Hatch-Waxman Amendments before. In *Abbott Laboratories v. Young*, we held that the parenthetical "(including any ester or salt of the active ingredient)" in § 355(j) could refer to "*either* the active ingredient of the original approved drug *or* to the active ingredient in the new drug."[7] 920 F.2d at 987. Each side claims support from *Abbott*. This is partly because the *Abbott* opinion was not entirely clear about what "active ingredient" means under § 355(j)(5)(F). At one point the *Abbott* opinion referred to "active ingredient" as "the substance prior to the introduction into the human body." *Id.* at 986. But then the court based its holding, in part, on the potential ambiguity of that phrase. *See id.* at 987-88. *Abbott* certainly did not adopt an interpretation of "active ingredient" that "unambiguously foreclose[d]" the agency's current approach. *Nat'l Cable & Telecomm. Ass'n v. Brand X Internet Servs.*, 545 U.S. 967, 983 (2005).

Neither does the structure or purpose of § 355(j) foreclose the agency's interpretation. The Hatch-Waxman Amendments "struck a balance between expediting generic drug applications and protecting the interests of the original drug manufacturers." *Abbott Labs.*, 920 F.2d at 985. Actavis argues that the FDA's current approach violates the statutory scheme, which it claims "reserves five-year exclusivity only for major innovations."

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[7] *Abbott* dealt with another exclusivity provision, then codified at 21 U.S.C. § 355(j)(4)(D)(i), that governed drugs approved between January 1, 1982, and September 24, 1984. The relevant language is identical to that in current § 355(j)(5)(F)(ii).

Actavis Br. 37. In this view, a drug containing a derivative molecule such as lisdexamfetamine should be entitled, at most, to three years of exclusivity. To buttress its claim, Actavis offers a scenario in which drug companies such as Shire are able to maintain never-ending periods of five-year exclusivity for "minor" variations on already approved drug molecules simply by adding different covalent appendages to them. Actavis Br. 42-43.

Shire is right that "Actavis' structural arguments represent little more than question-begging." Shire Br. 27. In the FDA's view, drug derivatives such as lisdexamfetamine *are* "major innovations" deserving five-year exclusivity. The FDA's regulations leave many types of drug derivatives eligible only for three-year exclusivity. For example, an ester derivative of a previously approved drug molecule remains entitled to three-year exclusivity if the application required for its approval "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(j)(5)(F)(iii). The FDA is *defining* the line between three- and five-year exclusivity, not eviscerating it.

Actavis' prediction of multiple repeated periods of five-year exclusivity for minor variations on existing drug products assumes a view (contrary to the agency's) of what constitutes a minor variation. It also finds little support in reality. In the nearly two decades since the current FDA regulations came into effect, there is no such example, or at least none Actavis has identified. This is hardly surprising, given the time and effort required to gain approval under § 355(b). *See Teva Pharm., USA, Inc., v. Leavitt*, 548 F.3d 103, 104 (D.C. Cir. 2008).

Since nothing in the text, structure, purpose, or legislative history of the statute "speaks directly to the precise question at

issue," the agency's interpretation must stand if it is reasonable. *Citizens Coal Council v. Norton*, 330 F.3d 478, 481 (D.C. Cir. 2003); *see also Brand X*, 545 U.S. at 986.

The FDA's policy is based on its view that drug derivatives containing non-ester covalent bonds are, on the whole, distinct from other types of derivative drugs such that the former are uniquely deserving of "new chemical entity" status and the resulting five-year exclusivity. The FDA explained its distinction in a 1989 response to a citizens' petition:

> It has been FDA's longstanding experience that even minor covalent structural changes are capable of producing not only major changes in the activity of a drug but changes that are not readily predicted . . . . In contrast to most changes in the covalent structure of a molecule, the formation of a salt or a complex, or of an ester, is not intended to, and generally cannot, alter the basic pharmacologic or toxicologic properties of the molecule . . ..

We are hard pressed to second-guess the FDA's view, especially since it "rests on the agency's evaluations of scientific data within its area of expertise." *Serono Labs., Inc. v. Shalala*, 158 F.3d 1313, 1321 (D.C. Cir. 1998) (internal quotation marks omitted). At best, Actavis has offered evidence that some covalent structural changes do not alter the basic properties of the drug in question and that some noncovalent structural changes do. But agencies may "employ bright-line rules for reasons of administrative convenience, so long as those rules fall within a zone of reasonableness and are reasonably explained." *Emily's List v. Fed. Election Comm'n*, 581 F.3d 1, 22 n.20 (D.C. Cir. 2002). The FDA has explained that its policy is based in part on the "difficulty in determining precisely which molecule, or portion of a molecule, is responsible for a drug's effects."

Nothing in the record establishes that the FDA's approach is unreasonable. Given the complexity of the statutory regime, we defer to the agency's interpretation. *See Cmty. Care Found. v. Thompson*, 318 F.3d 219, 225 (D.C. Cir. 2003).

III

Actavis has other arguments designed to show that the FDA's grant of five-year exclusivity to Vyvanse was "arbitrary [and] capricious." 5 U.S.C. § 706(2)(A). Primary among these is that the Vyvanse decision was in tension with past agency decisions, which, Actavis claims, establish that the FDA generally followed an "activity-based" approach to five-year exclusivity under the Hatch-Waxman Amendments. We do not consider it necessary to go into the details of these prior decisions. None of them rendered the FDA's grant of exclusivity to Vyvanse arbitrary and capricious.

The district court's grant of summary judgment to the FDA and to Shire is affirmed.

So ordered.