United States Court of Appeals
FOR THE DISTRICT OF COLUMBIA CIRCUIT

Argued October 24, 2005 Decided January 27, 2006

No. 04-5414

NOVARTIS PHARMACEUTICALS CORPORATION,
APPELLANT

v.

MICHAEL O. LEAVITT,
SECRETARY OF HEALTH AND HUMAN SERVICES, AND
LESTER M. CRAWFORD, JR.,
ACTING COMMISSIONER OF FOOD AND DRUGS,
APPELLEES

Appeal from the United States District Court
for the District of Columbia
(No. 99cv00323)

John M. Engel III argued the cause and filed the briefs for appellant.

Drake Cutini, Attorney, U.S. Department of Justice, argued the cause for appellees. With him on the brief were *Peter D. Keisler*, Assistant Attorney General, *Eugene M. Thirolf, Jr.*, Director, *Alex M. Azar II*, General Counsel, U.S. Department of Health and Human Services, *Eric M.*

Blumberg, Deputy Chief Counsel, and *Karen E. Schifter*, Associate Chief Counsel.

Before: TATEL and GRIFFITH, *Circuit Judges*, and WILLIAMS, *Senior Circuit Judge*.

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

WILLIAMS, *Senior Circuit Judge*: Securing FDA approval for a generic drug is generally a much simpler and faster process than securing approval for a "pioneer" drug. Instead of directly demonstrating the drug's safety and efficacy, see 21 U.S.C. § 355(a), manufacturers of the generic file an abbreviated new drug application ("ANDA") that need show only that the generic is the same as the pioneer drug along certain dimensions. See § 355(j)(2)(A)(i)-(viii). This case concerns FDA's decision to change the dosage forms, labeling, and established names associated with appellant Novartis's pioneer drug in ways that would ease the path for competing generic drugs. Novartis raises a number of procedural and substantive challenges to FDA's changes. The district court rejected all and we affirm.

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The fastest route to FDA approval requires an ANDA to demonstrate not only that a generic drug has the same active ingredient(s) as the pioneer drug and is bioequivalent to it, *i.e.*, roughly speaking, is absorbed at the same rate and to the same extent when administered under similar conditions, but also that the generic and pioneer drugs have the same dosage form and labeling. 21 U.S.C. § 355(j)(2)(A)(ii)-(v). The latter two requirements are at issue in this case.

"Dosage forms" are categories that relate to such matters as a drug's appearance, physical form, and method of administration. The FDA assigns each drug a dosage form; currently there are 77 such categories. See FDA, APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS Appx. C (25th ed. 2005). Some of the dosage forms are quite broad (for example, "elixir" or "tablet, chewable"), while others are relatively narrow (for example, "injectable, lipid complex"). *Id*. If a generic manufacturer cannot show that its drug has the same dosage form as the pioneer drug, it can still obtain FDA approval, but the process is more arduous: the manufacturer may use an abbreviated application only if it first files a "suitability petition" and the FDA grants it permission to file an ANDA. 21 U.S.C. § 355(j)(2)(C); 21 C.F.R. § 314.93. Even if the drug is ultimately approved, the difference in dosage form will preclude the generic from being designated therapeutically equivalent to the pioneer drug, and will thus disqualify the generic from being considered automatically substitutable for the pioneer drug under various state pharmacy laws. See *Warner-Lambert v. Shalala*, 202 F.3d 326, 327-28 (D.C. Cir. 2000).

To avoid charges of misbranding, the labels of prescription drugs must include certain pieces of information displayed in a particular way. See 21 U.S.C. § 352. Thus the requirement that a generic have the same labeling as the pioneer drug incorporates several additional requirements, two of which are relevant to this case.[1] First, FDA requires the

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[1] The same-label requirement excepts differences required because the generic was approved under a suitability petition or "because the new drug and the listed drug are produced or

labels to contain the pioneer drug's dosage form, see 21 C.F.R. § 201.57(a)(1)(ii), so the same-label requirement reincorporates the requirement that the generic drug share the pioneer drug's dosage form. Second, the FDA requires prescription drug labels to include the drug's established name, see 21 C.F.R. § 201.57(a)(1)(i), which is a nonproprietary name assigned to the drug by the FDA. The rule mandating inclusion of the established nonproprietary name on the label means that a generic drug must have the same nonproprietary name as the pioneer drug for the FDA to approve the generic drug through the ANDA process. We turn later to the statutory framework for assigning such names.

Novartis markets cyclosporine drug products that are widely prescribed to prevent organ rejection in kidney, liver, and heart transplants. (These drugs were developed by Novartis's predecessor, Sandoz Corp. For simplicity, we refer to both corporations as Novartis.) It markets two types of cyclosporine drugs under the proprietary names Sandimmune and Neoral. Both are available as capsules and as solutions, and both form emulsions when they come into contact with aqueous liquids. The difference is the size of the droplets in which the active ingredient is dispersed. Sandimmune forms a macroemulsion and disperses cyclosporine in larger droplets than does Neoral, which forms a microemulsion. The smaller size of the droplets in the microemulsion allows Neoral's active ingredient—cyclosporine—to be absorbed more quickly and efficiently in the gastrointestinal tract. See FDA

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distributed by different manufacturers." 21 U.S.C. § 355(j)(2)(A)(v); 21 C.F.R. § 314.94(a)(8)(iv).

Docket No. 96-P-0459, Response to Petition Filed by Novartis Pharmaceuticals Corp., at 4 (Nov. 2, 1998) ("Petition Response"). This difference means that the Sandimmune and Neoral products are not bioequivalent (*i.e.*, they are bioinequivalent) and that a physician's decision to switch a patient from one to the other may require a different prescription.

To highlight the differences between Sandimmune and Neoral, the FDA initially incorporated the term "microemulsion" into both Neoral's established name and its dosage form. When the FDA approved the Neoral products in 1995, it assigned them the established names "cyclosporine oral solution for microemulsion" and "cyclosporine capsules for microemulsion." Petition Response at 5; see also Joint Appendix 966-67. Shortly thereafter, the FDA created two new dosage forms and assigned them to the Neoral products: "capsule, microemulsion" and "solution, microemulsion."

At a symposium in December 1997 a leading transplant physician made a presentation about the development of a generic version of Neoral that formed a micro*dispersion* of solid particles instead of a microemulsion. Alarmed, Novartis filed a citizen petition in March 1998 requesting that the FDA not approve any generic with a dosage form that was not identical to Neoral's, or at least that it require an applicant seeking approval of such a drug to first file a suitability petition. (Novartis had previously filed another citizen petition, which the FDA denied in the same response as it denied the March 1998 petition; Novartis hasn't appealed denial of the first petition.) In principle the petition was simply a request that the FDA obey the law, though it could be taken as implicitly urging the FDA not to delete "microemulsion" from the dosage forms assigned to the

Neoral products. In fact the FDA did just what Novartis sought to avoid.

Responding to the petition in November 1998, the FDA announced that it would eliminate the microemulsion dosage forms altogether. It explained that it had determined that Neoral's ability to form a microemulsion was not a function of dosage form; rather than being an aspect of the "physical recognition, appearance, dosing and manner of administration," the microemulsion-forming feature of Neoral appeared only after the patient swallowed the product (or, in the case of the oral solution, mixed it with another beverage to make it more palatable) and was therefore a characteristic of the product's "formulation." Petition Response at 12-13 & n.14. There is no requirement that a generic drug have the same formulation as its pioneer. Moreover, the FDA said, elimination of the microemulsion dosage form would serve its policy goal of encouraging the availability of generic products. *Id*. at 14. Finally, it said that in light of its dosage form ruling it had reexamined the Neoral products' established names and determined that they should no longer refer to microemulsion. The new established names would be simply "cyclosporine capsules" and "cyclosporine oral solution." These names would apply to Sandimmune, to Neoral, and to any approved generic versions of Neoral that formed either microemulsions or microdispersions. To communicate the differences between Sandimmune on the one hand and Neoral and generic equivalents that form either microemulsions or microdispersions on the other, FDA said it would now require the label for Neoral and its generic equivalents to include the term "MODIFIED." Petition Response at 17. This term, explained the FDA, "is appropriate to alert physicians, pharmacists, and patients that Neoral's formulation presents a different bioavailability

profile than the Sandimmune formulation," and "is broad enough to encompass different, bioequivalent formulations of cyclosporine (e.g., a microemulsion or microdispersion) and, prominently displayed in bold type, the term may become readily associated with the more bioavailable formulations of cyclosporine." *Id*.

The FDA issued this decision around the time that it approved an ANDA for SangCya, a generic cyclosporine solution manufactured by SangStat Medical Corp. SangStat had submitted data purporting to show that SangCya was bioequivalent to Neoral. SangCya differed from Neoral in precisely the way that Novartis had anticipated a generic competitor might: it formed a microdispersion of solid particles instead of a microemulsion. Had the Neoral products' dosage forms, labeling, and established names continued to refer to microemulsion, SangStat would not have been able to secure FDA approval for SangCya by directly filing an ANDA.

A few months later, in February 1999, Novartis filed suit in district court raising challenges to the FDA's approval of the SangCya ANDA as well as to the FDA's modifications to Neoral's dosage forms, labeling, and established names. The district court found that the first of these challenges was moot: While this litigation was before the district court, new evidence came to light revealing that SangCya was not bioequivalent to Neoral when properly administered with apple juice instead of with chocolate milk, and the FDA withdrew its approval of SangCya. (FDA reports that as of the time it submitted its reply brief, there were eight approved and not withdrawn generic equivalents for Neoral, half of which form microemulsions. Br. for Appellee 11. Presumably the other half form microdispersions.) We affirm

the district court's conclusion that the withdrawal mooted Novartis's challenge to that approval for the reasons given by the district court. Mem. Op. (Mar. 5, 2001) 5-9.

On subsequent cross-motions for summary judgment, the district court rejected the challenges to the FDA's disposition of Novartis's citizen petition. Mem. Op. (Sept. 9, 2004). We affirm the district court's rejection of each of Novartis's substantive challenges to the FDA's decisions regarding dosage forms, labeling, and established names of its Neoral products. Because we have nothing to add to the district court's reasoning on these issues, we do not address them here. We do address below Novartis's challenges to the completeness of the administrative record and to the procedures employed by the FDA to change Neoral's dosage forms, labeling, and established names. In each case, we affirm the district court.

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The first objection that Novartis raises on appeal is that the district court erred by failing to require production of the "whole record" as required by the Administrative Procedure Act. We review the district court's refusal to supplement the administrative record for abuse of discretion. See *James Madison Ltd. v. Ludwig*, 82 F.3d 1085, 1095 (D.C. Cir. 1996).

There are actually two administrative records at issue in this case. The first is the public docket for Novartis's citizen petition, the second is the record of the FDA's approval of the SangCya ANDA. The district court initially referred the question of the records' proper scope to a magistrate judge, who refused Novartis's requests to supplement the citizen petition record with records from a group of prior proceedings

that Novartis claimed were relevant, finding that FDA did not consider these records in addressing the citizen petition. Mem. Op. (Jan. 18, 2000) 5-8. The magistrate judge did provide Novartis with the SangCya ANDA approval record after withholding some trade-secret, confidential-commercial, and otherwise privileged information. *Id*. at 8-11. The district court affirmed the magistrate judge's determinations. Mem. Op. (May 4, 2000).

When the new evidence concerning SangCya's bioinequivalence became available, Novartis again sought to supplement the record. The magistrate judge agreed with Novartis in part, expanding the record to include both the new bioinequivalence data and the hitherto withheld portions of SangCya's ANDA relating to its asserted bioequivalence. Mem. Op. (Nov. 27, 2000). In a subsequent decision the district court addressed both SangStat's motion to dismiss Novartis's challenge to the SangCya approval (by then withdrawn) as moot and SangStat's separate motion to reconsider the magistrate judge's determination regarding the scope of the record. The district court found that Novartis's attack on the SangCya approval was moot, Mem. Op. (Mar. 5, 2001) 5-9; as noted above, we affirm that decision for the reasons stated. The district court then vacated the magistrate judge's expansion of the record, regarding its decision on substantive mootness as controlling that issue. *Id*. at 9.

On appeal, Novartis renews the supplementation requests denied by the district court. In making its case Novartis relies heavily on *American Bioscience, Inc. v. Thompson*, 243 F.3d 579 (D.C. Cir. 2001), and *Walter O. Boswell Memorial Hosp. v. Heckler*, 749 F.2d 788 (D.C. Cir. 1984). These cases do little to support Novartis's position. The agency failed to file any administrative record at all in the former case, *American*

Bioscience, Inc., 243 F.3d at 582, while in the latter neither party purported to have provided the court with the complete administrative record, *Walter O. Boswell Memorial Hospital*, 749 F.2d at 792. We find no abuse of discretion in the district court's holding that the administrative record was complete and sufficient for judicial review; we adopt its reasoning except with respect to Novartis's efforts to include the data that originally purported to establish SangCya's bioequivalence to Neoral. Rather than resting on the mootness of Novartis's challenges to SangCya's approval, we rely on the district court's later finding that Novartis has pointed to nothing to support its claim that the FDA's approval of SangCya tainted its consideration of the logically distinct issues raised by Novartis's own citizen petition. See Mem. Op. (Sept. 9, 2004) 26-27. Novartis makes one other claim about the record, but because it is closely related to Novartis's procedural challenge to the FDA's modifications of the Neoral products' established names, we address it in the next section.

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Novartis raises two procedural objections that apply to each of the FDA's decisions regarding Neoral's dosage forms, labeling, and established names, and a third procedural objection that applies only to the FDA's modification of the established names for the two Neoral products. These challenges rely, in varying proportions, on interpretations of the Federal Food, Drug, and Cosmetic Act ("FDCA") and regulations interpreting that statute. We have held on a number of occasions that FDA interpretations of the FDCA receive deference, as do its interpretations of its own regulations unless plainly erroneous or inconsistent with the

regulations. See, *e.g.*, *Purepac Pharmaceutical Co. v. Thompson*, 354 F.3d 877, 883 (D.C. Cir. 2004); *Mova Pharmaceutical Corp. v. Shalala*, 140 F.3d 1060, 1071 n.13 (D.C. Cir. 1998).

First, Novartis objects to the FDA's failure to publicly docket any of SangStat's requests that the FDA modify the dosage forms, labeling, and established names that apply to Novartis's Neoral products, saying that the FDA violated its own procedures by not treating those requests as citizen petitions. See 21 C.F.R. § 10.30. The district court held that the provision permitting an interested person to petition the FDA "does not require FDA to convert every letter or telephone call it receives in conjunction with an ANDA into a citizen petition." Mem. Op. (Sept. 9, 2004) 24. And, the district court pointed out, another regulation forbids the FDA from disclosing information about a pending ANDA unless its existence has previously been publicly disclosed. *Id*. (citing 21 C.F.R. § 314.430(b)-(c)). We affirm.

Second, Novartis insists that the FDA erred by failing to provide Novartis with notice or opportunity to comment on its decisions. The district court disagreed, pointing out that Novartis's own citizen petition gave it an opportunity to show, in detail, why it believed that the microemulsion dosage forms were appropriate. Mem. Op. (Sept. 9, 2004) 25. We also note that Novartis acknowledged the link between dosage form and labeling in that same petition and that the public docket indicates Novartis took advantage of its opportunity to respond to comments made by others in response to its petition. As Novartis received ample notice and opportunity to be heard, it has already received every benefit that it could from a favorable judgment on this issue. *Better Government*

Ass'n v. Department of State, 780 F.2d 86, 91 & n.21 (D.C. Cir. 1986).

Third, Novartis makes a more specific argument that the FDA's actions in modifying the Neoral products' established names were not procedurally proper. Our analysis of this argument is more complicated because Novartis and the FDA disagree on how to characterize the status of the nonproprietary names assigned to the Neoral products when the FDA approved them in 1995. Novartis argues that the FDA designated "official" names pursuant to 21 U.S.C. § 358(a). This is significant, Novartis argues, because it means that the FDA may not modify those names without undertaking notice-and-comment rulemaking. We conclude that Novartis fails to establish either that the FDA was required to proceed under § 358, or that as a discretionary matter it did proceed under that section, in originally establishing nonproprietary names for the Neoral products in 1995.

To evaluate Novartis's arguments regarding the FDA's initial assignment of nonproprietary names, we begin by reviewing the statutory and regulatory framework governing established names. There are two key statutory provisions. The first is 21 U.S.C. § 352(e)(1)(A)(i), which provides that a drug may be subject to charges of misbranding unless its label bears, among other things, "the established name (as defined in subparagraph (3)) of the drug, if there is such a name." Subparagraph (3) provides that "established name" means:

> (A) the applicable official name designated pursuant to section 358 of this title, or

> (B), if there is no such name and such drug, or such ingredient, is an article recognized in an official compendium, then the official title thereof in such compendium, or
>
> (C) if neither clause (A) nor clause (B) of this subparagraph applies, then the common or usual name, if any, of such drug or of such ingredient [with an exception that is not relevant here].

21 U.S.C. § 352(e)(3). Neither party argues that clause (C) applies to the name given Novartis's products in 1995, and they affirmatively agree that clause (B) didn't apply to those designations. See Mem. Op. (Sept. 9, 2004) 28 n.12. The "official compendium" referred to in clause (B) is the United States Pharmacopoeia ("USP"); the applicable article (or monograph) titles in the USP omit the term "microemulsion."

Reasoning by process of elimination, Novartis argues that with clauses (B) and (C) out of the picture the FDA's 1995 action must have been a designation under clause (A) of § 352(e)(3). Br. for Appellants 34. But this hardly appears to be the only reasonable reading of the statute. For starters, § 352(e)(1)(A)(i) refers to an established name "*if there is such a name*," suggesting that the categories of established names set out in § 352(e)(3) do not exhaust the categories of nonproprietary names that the FDA might assign.[2]

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[2] The parties appear to assume that § 352(e)(1)(A)(i)'s labeling requirements encompass any nonproprietary name assigned to a drug by the FDA even if the name does not qualify under § 352(e)(3). We express no opinion on the issue.

Novartis tries to buttress its reading by asserting that § 352(e)(3) defines the three name categories in "descending order of preference." Br. for Appellants 34. Novartis seems to have no basis for the claim; every list puts some things lower than others, but order is not necessarily an indication of rank. Also, the FDA's regulations take quite a different position, providing that the FDA "will not routinely designate official names under section 508 of the act [21 U.S.C. § 358]. . . ." 21 C.F.R. § 299.4(e).

The second key statutory provision is § 358. Subsection (a) provides:

> The Secretary may designate an official name for any drug or device if he determines that such action is necessary or desirable in the interest of usefulness and simplicity. Any official name designated under this section for any drug or device shall be the only official name of that drug or device used in any official compendium published after such name has been prescribed or for any other purpose of this chapter.

21 U.S.C. § 358(a). Section 358(b) requires the Secretary to undertake an apparently comprehensive review of the names by which drugs are identified in official compendia—*i.e.*, in the USP. Section 358(c) provides that if, after such a review, the Secretary determines that any names in the USP are problematic in any of several specified ways, the Secretary will initiate a notice-and-comment rulemaking to replace them with new names.

Novartis's argument that the FDA in fact designated an official name pursuant to § 358 runs into trouble because the FDA's 1995 actions didn't align with the requirements of

§ 358. First, there is no indication that the comprehensive review described in § 358(b), at least arguably a prerequisite to a § 358 designation, ever occurred. Second, as the district court pointed out, § 358(c) requires the agency to designate the official names through notice-and-comment rulemaking, which wasn't done in 1995. Novartis argues that the notice-and-comment requirement was satisfied because the FDA designated names for Novartis's Neoral products "at the conclusion of a formal process involving consultation with the USP [Nomenclature Committee] and rejection of the existing USP compendial name," Br. for Appellant 34, but it never explains why those procedures should be considered interchangeable with notice-and-comment rulemaking. Nor did the FDA publicly indicate in some other way in 1995 that it was designating an official name under § 358. Third, § 358(a) requires that once the FDA designates an official name, that name must be used in any official compendium. But, as explained above, the USP Nomenclature Committee did not adopt the nonproprietary names that the FDA assigned to Neoral in 1995. Novartis disregards this statutory requirement. Accordingly, there is no reason to believe such a designation occurred. Cf. Mem. Op. (Sept. 9, 2004) 28-29.

Finally, Novartis contends that whether the FDA assigned official names pursuant to § 358 is a factual question that cannot be answered without supplementing the administrative record with documentation of the FDA's actions when it originally approved nonproprietary names for the Neoral products. We see no need for such an excavation. Given the gaps identified above, there is no serious likelihood that extra documentation of the process by which the FDA developed the nonproprietary names it initially assigned to the Neoral would overturn our conclusion that the FDA did not proceed under § 358.

Having rejected Novartis's characterization of the FDA's actions in 1995, we examine the agency's explanation of the names it then assigned to the Neoral products as "interim established names." The FDA argues that the reference in § 352(e)(1)(A)(i) to a drug's established name, "if there is such a name," means that it was not limited to the options set out in § 352(e)(3) in designating a nonproprietary name. It explains that it had filled that statutory gap by creating a fourth category of names for drug products: "interim established names." Recall that under § 352(e)(3) a drug product's established name could be the official monograph title for that product in the USP. The USP Nomenclature Committee acts on its own schedule, so that its designation of a name qualifying under § 352(e)(3)(B) need not coincide with the FDA's approval of a drug. Mem. Op. (Sept. 9, 2004) 29-30. Given the variable sequence, the FDA's designation of "interim" or "provisional" established names outside the § 352(e)(3) triad appears both consistent with the statutory structure and reasonable.

As the statute leaves space for FDA designation of interim or provisional established names, Novartis has no basis for claiming that § 358 commands a notice-and-comment rulemaking for the change of such a name. And Novartis makes no claim that the APA itself commands use of that specific procedure in the absence of a § 358 designation. Insofar as Novartis makes a general claim that FDA acts arbitrarily and capriciously by not providing adequate notice and opportunity for comment before making any change of the Neoral products' interim names, our earlier observation controls: Novartis had ample notice and opportunity to comment in its own citizen petition proceeding.

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The judgment of the district court is

Affirmed.