

**PUBLISHED**

**UNITED STATES COURT OF APPEALS**

**FOR THE FOURTH CIRCUIT**

ZENECA, INCORPORATED,

Plaintiff-Appellant,

v.

DONNA E. SHALALA, in her official  
capacity as Secretary of Health and

Human Services; JANE HENNEY,

M.D., Commissioner of the Food

and Drug Administration,

Defendant-Appellees.

No. 99-2329

v.

GENSIA SICOR PHARMACEUTICALS,

INCORPORATED,

Movant-Appellee.

Appeal from the United States District Court  
for the District of Maryland, at Baltimore.

William M. Nickerson, District Judge.

(CA-99-307-WMN)

Argued: April 5, 2000

Decided: May 17, 2000

Before NIEMEYER, Circuit Judge,

HAMILTON, Senior Circuit Judge, and

Roger J. MINER, Senior Circuit Judge of the

United States Court of Appeals for the Second Circuit,

sitting by designation.

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Affirmed by published opinion. Senior Judge Hamilton wrote the  
opinion, in which Judge Niemeyer and Senior Judge Miner joined.

## COUNSEL

Anthony Craig Roth, MORGAN, LEWIS & BOCKIUS, L.L.P., Washington, D.C., for Appellant. Gerald Cooper Kell, Senior Trial Counsel, Office of Consumer Litigation, UNITED STATES DEPARTMENT OF JUSTICE, Washington, D.C., for Appellees Shalala and Henney; David Glenn Adams, VENABLE, BAETJER, HOWARD & CIVILETTI, L.L.P., Washington, D.C., for Appellee Gensia Sidor. **ON BRIEF:** Stephen P. Mahinka, MORGAN, LEWIS & BOCKIUS, L.L.P., Washington, D.C., for Appellant. David W. Ogden, Acting Assistant Attorney General, Office of Consumer Litigation, UNITED STATES DEPARTMENT OF JUSTICE, Washington, D.C.; Barbara J. Stradling, Associate Chief Counsel for Enforcement, FOOD AND DRUG ADMINISTRATION, Washington, D.C., for Appellees Shalala and Henney. James N. Czaban, VENABLE, BAETJER, HOWARD & CIVILETTI, L.L.P., Washington, D.C., for Appellee Gensia Sidor.

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## OPINION

HAMILTON, Senior Circuit Judge:

This case involves a challenge by appellant Zeneca, Inc. (Zeneca), the manufacturer of the prescription drug DIPRIVAN, to the Food and Drug Administration's (the FDA) approval of a generic version of DIPRIVAN manufactured by intervenor-appellee Gensia Sidor Pharmaceuticals, Inc. (Gensia). The district court granted Gensia's and the FDA's motions for summary judgment. Because we agree with the district court that the FDA's approval of Gensia's generic drug was in accordance with the Federal Food, Drug and Cosmetic Act (the FDCA), 21 U.S.C.A. §§ 301-397 (West 1999), and the FDA's own regulations implementing the FDCA, we affirm.

I

A

The FDCA requires drug manufacturers to obtain FDA approval prior to marketing new drugs. See id. § 355. To obtain FDA approval,

the first applicant to market a drug--the "pioneer"--must submit a New Drug Application (NDA) to the FDA containing, among other things, "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," and "specimens of the labeling proposed to be used for such drug." Id. § 355(b)(1). The FDA's primary role in the NDA process is to ensure that the drug manufacturer has proven that its new drug (the pioneer drug) is safe and effective prior to marketing. See generally id. § 355(d).

Once the FDA has "listed" a pioneer drug as approved, the FDCA allows any person or entity desiring to market a generic copy of the pioneer drug to seek FDA approval of its generic version through an Abbreviated New Drug Application (ANDA). See id. § 355(j). The ANDA procedure "permits generic drug applications to piggy-back on clinical findings that [the] FDA has already embraced" in the NDA, In re Barr Labs., Inc., 930 F.2d 72, 73 (D.C. Cir. 1991), and thus, the ANDA applicant need not duplicate the clinical safety studies that supported the pioneer drug's NDA. The ANDA process, however, does not absolve the generic drug manufacturer from its burden of establishing that its generic drug is the bioequivalent of the pioneer drug, see 21 U.S.C.A. § 355 (j)(2)(A)(iv), (4)(F), and is safe and effective, see id. § 355(j)(2)(A)(iv), (4)(H).<sup>1</sup>

In order to obtain approval of a generic drug, a manufacturer must provide information sufficient to establish that, among other things: (1) the generic drug is "bioequivalent" to the pioneer drug; (2) its active ingredients, route of administration, strength and dosage form are "the same as" those of the pioneer drug; and (3) the inactive ingredients are not "unsafe for use under the conditions prescribed, recommended, or suggested in the labeling proposed for the drug." Id. §§ 355(j)(4)(C), (D), (H). With respect to the substitution of inactive ingredients in a parenteral drug,<sup>2</sup> the FDA's regulations require that

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<sup>1</sup> From the structure of § 355(j), it is evident that subsection 355(j)(2) explicates the required information a would-be generic drug manufacturer must provide in its ANDA. Subsection 355(j)(4), on the other hand, provides the parameters for the FDA's review of the information submitted under subsection 355(j)(2) and its authority to deny an ANDA.

<sup>2</sup> Parenteral means "[b]y some other means than through the gastrointestinal tract: referring particularly to the introduction of substances into an organism by intravenous, subcutaneous, intramuscular, or intramedullary injection." Stedman's Medical Dictionary 1316 (1999).

most of the generic drug's inactive ingredients be the same as the inactive ingredients of the pioneer drug. Differences in inactive ingredients that are preservatives, buffers, or antioxidants are permitted as long as those differences do not affect the safety of the drug. See 21 C.F.R. §§ 314.94(a)(9)(iii), 314.127(a)(8)(ii)(B) (1999).

Manufacturers of generic drugs are also required to show that "the labeling proposed for the new [generic] drug is the same as the labeling approved for the listed drug . . . except for changes required . . . because the new drug and the listed drug are produced or distributed by different manufacturers." 21 U.S.C.A. § 355(j)(2)(A)(v); see also id. § 355(j)(4)(G). This "same labeling" requirement has been interpreted by the FDA to require that

[l]abeling . . . proposed for the [generic] drug product must be the same as the labeling approved for the reference listed drug, except for changes required . . . because the drug product and the reference listed drug are produced or distributed by different manufacturers. Such differences between the applicant's proposed labeling and labeling approved for the referenced listed drug may include differences in expiration date, formulation, bioavailability, or pharmacokinetics, labeling revisions made to comply with current FDA labeling guidelines or other guidance, or omission of an indication or other aspect of labeling protected by patent or accorded exclusivity under section 505(j)(4)(D) of the act.

21 C.F.R. § 314.94(a)(8)(iv) (emphasis added).

## B

Zeneca manufactures the pioneer drug DIPRIVAN (a form of propofol), which the FDA approved in 1989 based on Zeneca's submission of an NDA. DIPRIVAN is a parenteral drug used for inducing and maintaining anesthesia and for support of mechanical ventilation and sedation. DIPRIVAN has a pH range of 7.0 to 8.5. Shortly after Zeneca introduced DIPRIVAN in the United States, post-operative fevers and infections were documented and associated with its use. These post-operative fevers and infections were determined to be the result of microbial contamination caused by mishan-

dling of the drug by medical personnel. With the FDA's encouragement, Zeneca decided to reformulate DIPRIVAN by adding the preservative disodium edetate (EDTA) in order to prevent microbial contamination. Zeneca performed clinical studies on the safety of the reformulated DIPRIVAN and, in return, was awarded three years of exclusivity for the reformulated DIPRIVAN when it was approved in 1996.

In March 1997, Gensia submitted an ANDA to the FDA for approval of a generic propofol product with EDTA, the same composition as DIPRIVAN. In July 1997, Gensia informed the FDA that it was evaluating the development of propofol using the preservative sodium metabisulfite (Sulfite) instead of EDTA.<sup>3</sup> In its July 1997 letter, Gensia provided preliminary data on a propofol product with Sulfite that would have a pH range of 6.0 to 7.5.<sup>4</sup> Gensia asked the FDA to review the preliminary data and consider, in particular, the proposed lower pH of Gensia's formulation and the safety of Sulfite as a preservative. The Office of Generic Drugs (the OGD) undertook a review of the preliminary data.<sup>5</sup> In addition, the FDA's Division of Anesthetic, Critical Care and Addiction Products, the division that reviewed and approved the NDA for DIPRIVAN, provided consultation to the OGD about the proposed propofol product containing Sulfite. On January 16, 1998, Gensia withdrew its ANDA for propofol with EDTA and submitted an ANDA for propofol with Sulfite (Gensia's ANDA for propofol with Sulfite) with a new proposed pH range of 4.5 to 6.4.

On April 7, 1998, after learning that the FDA was considering an ANDA for generic propofol, Zeneca filed an administrative petition for a stay of action pursuant to 21 C.F.R. § 10.35 (1999). Zeneca's petition requested, among other things, that the FDA decline to approve any generic version of DIPRIVAN that "contains an antimi-

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<sup>3</sup> Sulfite is a preservative, which is an inactive ingredient under the FDCA. See 21 C.F.R. §§ 314.94(a)(9)(iii), 314.127(a)(8)(ii)(B).

<sup>4</sup> To ensure that its propofol with Sulfite would achieve a microbial growth retardation similar to DIPRIVAN, Gensia eventually had to adjust the pH to the 4.5 to 6.4 range.

<sup>5</sup> OGD is the office within the FDA that receives, reviews, and approves ANDAs. See 21 C.F.R. § 5.80(c)(1)(i).

crobial additive other than [EDTA], the safety of which is not supported by preclinical, clinical, or other scientific investigative studies." (J.A. 684). Zeneca contended that the substitution of Sulfite for EDTA and the lower pH of Gensia's propofol with Sulfite raised safety issues; specifically, issues of allergenicity, toxicity, antimicrobial effectiveness, and product stability. Further, Zeneca argued that the addition of a Sulfite warning required by 21 C.F.R. § 201.22 to the label of Gensia's propofol with Sulfite would violate the statutory "same labeling" requirement for generic drugs.

On January 4, 1999, the FDA approved Gensia's ANDA for propofol with Sulfite. On the same day, the FDA denied Zeneca's petition. The FDA noted that it "did not require clinical studies to establish the safety of [Gensia's] drug product; instead, the Agency found that sufficient information was available both in the ANDA and before the Agency to address whether changing the preservative to sodium metabisulfite compromised the safety of the propofol injectable emulsion product." (J.A. 689). The FDA concluded that it "had substantial data to evaluate the possible effects of sodium metabisulfite in propofol because sodium or potassium metabisulfite is present in concentrations ranging from 0.1 mg/ml to 10 mg/ml in more than 50 approved drug products." (J.A. 689-90). Based on the information in the administrative record and its scientific expertise, the FDA determined that the presence of Sulfite in Gensia's propofol did not affect the safety profile of the drug.

The FDA also concluded that Gensia's propofol with Sulfite was safe and therapeutically equivalent to DIPRIVAN. Of particular note, the FDA acknowledged that "patients with sulfite allergies should not be administered a formulation of propofol with [Sulfite]. Appropriate labeling, however, is sufficient to protect against improper use of the product." (J.A. at 694). Accordingly, the FDA required Gensia's propofol with Sulfite product to include a "statement in the insert labeling informing practitioners of precautions related to the presence of sulfites," and to "highlight prominently on the container label that the product contains [Sulfite]."<sup>6</sup> (J.A. 694). The FDA concluded that

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<sup>6</sup> The FDA's regulations require a warning statement to appear on package inserts for prescription drugs containing sulfites because "sul-

these warnings "serve to alert practitioners of the potential for allergic reactions and are adequate to ensure safe use of the drug." (J.A. 694). Based on the addition of these warnings to the label of Gensia's propofol with Sulfite, the FDA concluded that Gensia's propofol with Sulfite was a safe generic drug when properly administered to the majority of the population, which has no allergic reaction to Sulfites.

On February 5, 1999, Zeneca filed a complaint and a motion for a preliminary injunction in the United States District Court for the District of Maryland challenging the FDA's approval of Gensia's ANDA for propofol with Sulfite as arbitrary and capricious under § 706(2)(A) of the Administrative Procedure Act (the APA), 5 U.S.C.A. § 706(2)(A) (West 1996).<sup>7</sup> Zeneca primarily argued that the substitution of Sulfite for EDTA in Gensia's propofol raised safety concerns and required a label warning such that the drug could not be lawfully approved through an ANDA. Gensia sought, and was granted, permission to intervene as a defendant.

At a hearing on March 26, 1999, the district court, after hearing oral arguments, denied Zeneca's motion for a preliminary injunction. On April 15, 1999, Zeneca filed a motion for partial summary judgment. The FDA and Gensia filed cross-motions for summary judgment on the entire case on May 6 and 7, 1999, respectively. On August 12, 1999, the district court granted the FDA's and Gensia's motions for summary judgment. This timely appeal by Zeneca followed.

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fites may cause allergic-type reactions in certain susceptible persons, especially asthmatics." 21 C.F.R. § 201.22(a) (1999). The FDA's approval of Gensia's propofol with Sulfite also required the label to state "Contains Sulfite" and list "SODIUM METABISULFITE" as an ingredient. *Id.* § 201.22(b).

<sup>7</sup> The denial of Zeneca's administrative petition for a stay of action filed pursuant to 21 C.F.R. § 10.35 constitutes final agency action for purposes of judicial review under the APA, 5 U.S.C.A. §§ 701-706. *See* 21 C.F.R. § 10.45(d).

## II

On appeal, Zeneca makes three substantive arguments in support of its claim that the FDA's approval of Gensia's ANDA for propofol with Sulfite was arbitrary and capricious, and must therefore, be declared invalid and permanently enjoined. First, Zeneca argues that the FDA's approval of Gensia's ANDA for propofol with Sulfite violated two FDA regulations prohibiting the FDA from approving an ANDA for a generic drug with a different preservative than the pioneer drug where the information submitted by the generic drug manufacturer fails to show that the substitute preservative does not affect the safety of the proposed generic drug. Second, Zeneca argues that the FDA violated its own regulation requiring a generic drug's labeling to be the same, with some exceptions, as its pioneer counterpart. Finally, Zeneca argues that the FDA approved Gensia's ANDA for propofol with Sulfite based upon a flawed medical review of the safety of Gensia's propofol with Sulfite.

We review the district court's grant of summary judgment *de novo*. See Marshall v. Cuomo, 192 F.3d 473, 478 (4th Cir. 1999). Our review of the underlying FDA approval of Gensia's ANDA for propofol with Sulfite, however, is conducted pursuant to § 706(2)(A) of the APA, which provides in relevant part that a "reviewing court shall . . . hold unlawful and set aside agency action, findings, and conclusions found to be--(A) arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." 5 U.S.C.A. § 706(2)(A); see Marshall, 192 F.3d at 478. In determining whether agency action violates § 706(2)(A) of the APA, "we perform only the limited, albeit important, task of reviewing agency action to determine whether the agency conformed with controlling statutes, and whether the agency has committed 'a clear error of judgment.'" Maryland Dep't of Human Resources v. USDA, 976 F.2d 1462, 1475 (4th Cir. 1992) (quoting Baltimore Gas & Elec. Co. v. Natural Resources Defense Council, Inc., 462 U.S. 87, 97 (1983), and Citizens to Preserve Overton Park, Inc. v. Volpe, 401 U.S. 402, 416 (1971)). "[T]he ultimate standard of review is a narrow one. The court is not empowered to substitute its judgment for that of the agency." Citizens to Preserve Overton Park, 401 U.S. at 416.

With these principles of the standard of review in mind, we now turn to address each of Zeneca's three substantive arguments.

A

Zeneca first argues that the FDA violated 21 C.F.R. §§ 314.94(a)(9)(iii) and 314.127(a)(8)(ii)(B) by approving Genesia's ANDA for propofol with Sulfite without requiring Genesia to adequately show that the substitution of Sulfite for EDTA as a preservative did not affect the safety of the drug formula based on DIPRIVAN. Therefore, Zeneca argues, the FDA's approval was arbitrary and capricious. We conclude that Zeneca's argument is without merit.

Section 314.94(a)(9)(iii) permits substitution of preservatives in parenteral drugs "provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety of the proposed drug product." 21 C.F.R. § 314.94(a)(9)(iii). Similarly, section 314.127(a)(8)(ii)(B) provides, in relevant part, that the FDA will not approve an ANDA for a generic drug product "unless it contains the same inactive ingredients, other than preservatives . . . and, if it differs from the listed drug in a preservative . . . the application contains sufficient information to demonstrate that the difference does not affect the safety of the drug product." *Id.* § 314.127(a)(8)(ii)(B). Collectively, these regulatory sections establish that prior to approving an ANDA for a generic drug with a preservative that differs from the listed pioneer drug, the FDA must determine that the preservative does not affect the safety of the drug. In this case, the FDA concluded that the substitution of Sulfite for EDTA as a preservative did not affect the safety of Genesia's propofol because warnings on the product's container and labeling would "serve to alert practitioners of the potential for allergic reactions and are adequate to ensure safe use of the drug." (J.A. 694).

As an initial matter, we note that the use of Sulfites in prescription drugs is widespread. See Sulfiting Agents: Labeling in Drugs for Human Use; Warning Statement, 50 Fed. Reg. 47,558, 47,558 (1985) (proposed rule) (noting that, at that time, sulfites were present "in more than 1,100 oxygen-sensitive prescription drug products"). Moreover, the "FDA has not found evidence in the available information on sulfites in human drugs that demonstrates a significant health hazard to the general population." *Id.* at 47,560. Zeneca does not challenge this finding nor does it contest the FDA's determination that

"sulfites serve a necessary public health function by maintaining the potency of certain medications." Sulfiting Agents; Labeling in Drugs for Human Use; Warning Statement, 51 Fed. Reg. 43,900, 43,903 (1986) (final rule). Accordingly, the issue before us is not whether sulfites, in and of themselves, are safe. They are. Rather, the issue is whether the substitution of Sulfite for EDTA in Gensia's propofol with Sulfite affects the safety of Gensia's propofol with Sulfite. The FDA concluded that the substitution of Sulfite for EDTA in Gensia's propofol with Sulfite did not affect the safety of Gensia's propofol with Sulfite because warning labels obviated any potential risks.

Zeneca argues that the FDA's reliance upon warnings on the product's container and labeling in making its decision as to whether Gensia's propofol with Sulfite is safe for use is prohibited under the plain language of sections 314.94(a)(9)(iii) and 314.127(a)(8)(ii)(B). In other words, Zeneca argues, under the plain language of these two regulations, the FDA may not rely on an enhanced warning label to obviate the safety concerns associated with different preservatives.

In response, the FDA contends that Zeneca's argument is without merit, because it places an unreasonably narrow construction on the regulations at issue, regulations promulgated by the FDA.<sup>8</sup> In support of its contention, the FDA points to the plain language of 21 U.S.C. § 355(j)(4)(H), the statute the two regulations at issue were promulgated to implement, which expressly provides that under the ANDA process, the FDA's consideration of the safety of inactive ingredients in generic drugs is dependent upon: (1) the "conditions prescribed, recommended, or suggested in the labeling"; and (2) the "type or quantity of inactive ingredients included or the manner in which the inactive ingredients are included." 21 U.S.C.A. § 355(j)(4)(H).

Zeneca's argument challenges the FDA's interpretation of its own regulations, which interpretation "is entitled to `substantial deference' and will be sustained unless it is plainly erroneous or inconsistent with the regulation[s]." Clinchfield Coal Co. v. Harris, 149 F.3d 307, 309 (4th Cir. 1998). We find the FDA's interpretation of 21 C.F.R. §§ 314.94(a)(9)(iii) and 314.127(a)(8)(ii)(B) to be consistent with the

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<sup>8</sup> Because the FDA and Gensia represent the same interests in this appeal, we refer to them collectively as the FDA.

language of these regulations and not plainly erroneous. Specifically, the language of sections 314.94(a)(9)(iii) and 314.127(a)(8)(ii)(B) is broad enough to encompass the FDA's interpretation. Furthermore, the FDA's interpretation is completely faithful to the statute that these two regulations were promulgated to implement, 21 U.S.C.

§ 355(j)(4)(H).<sup>9</sup> See Abbreviated New Drug Application Regulations, 57 Fed. Reg. 17,950, 17,957, 17,968-69 (1992) (final rule); Abbreviated New Drug Application Regulations, 54 Fed. Reg. 28,872, 28,884 (1989) (proposed rule). In sum, we conclude the FDA acted in accordance with 21 C.F.R. §§ 314.94(a)(9)(iii) and 314.127(a)(8)(ii)(B) and 21 U.S.C. § 355(j)(4)(H). Thus, the FDA's approval of Gensia's ANDA for propofol with Sulfite was not arbitrary and capricious for the first reason argued by Zeneca.

## B

Next we address Zeneca's argument that the FDA violated its own regulation requiring a generic drug's labeling to be the same as its pioneer counterpart.

Section 355(j)(2)(A)(v) of the FDCA allows labeling differences that are necessary "because the new [generic] drug and the listed [pioneer] drug are produced or distributed by different manufacturers." 21 U.S.C.A. § 355(j)(2)(A)(v). The FDA has interpreted § 355(j)(2)(A)(v) to permit changes in labeling because of "differences in expiration date, formulation, bioavailability, or pharmacokinetics, [or] labeling revisions made to comply with current FDA labeling guidelines or other guidance." 21 C.F.R. § 314.94(a)(8)(iv) (emphasis added). In this case, the FDA interpreted 21 C.F.R. § 314.94(a)(8)(iv) to find that the Sulfite warning for Gensia's propofol with Sulfite fit squarely within the exceptions for (1) formulation differences and (2) differences required to comply with the labeling guidelines in the FDA's Sulfite warning regulation, see 21 C.F.R. § 201.22(b).

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<sup>9</sup> Section 355(j)(4)(H) is the only section in the FDCA's new drug approval process (both NDA and ANDA) that directly addresses the FDA's review of inactive ingredients. See generally 21 U.S.C.A. § 355(j).

Zeneca agrees that under section 314.94(a)(8)(iv) a generic drug's labeling may reflect differences in formulation but argues that the generic drug's labeling may only reflect differences in the components or ingredients of the drug and not safety risks associated with the components or ingredients. Zeneca also agrees that under section 314.94(a)(8)(iv) a generic drug's labeling may reflect differences required by the FDA's labeling guidelines but argues that, by its terms, this exception only applies to situations in which such guidelines are issued "after approval of the[pioneer] drug but before approval of the generic." (Appellant's Br. at 52).

Again, Zeneca's arguments challenge the FDA's interpretation of its own regulation, which interpretation "is entitled to `substantial deference' and will be sustained unless it is plainly erroneous or inconsistent with the regulation." Clinchfield Coal Co., 149 F.3d at 309. We find the FDA's interpretation of 21 C.F.R. § 314.94(a)(8)(iv) to be consistent with the language of the regulation and not plainly erroneous. The Sulfite safety warning in Gensia's labeling is a direct result of the difference in formulation between Gensia's propofol with Sulfite and DIPRIVAN. Gensia was fully authorized to formulate its generic drug with a different preservative than is contained in DIPRIVAN. See 21 U.S.C.A. § 355(j)(4)(H); 21 C.F.R. § 314.94(a)(9)(iii) (providing that "an applicant may seek approval of a [parenteral] drug product that differs from the reference listed drug in preservative" (emphasis added)). Because a difference in preservative is a permitted variation in formulation, it is reasonable for the FDA to interpret its own regulation to allow corresponding differences in labeling to identify the preservative and provide any appropriate warnings.

In addition to permitting labeling changes based on differences in formulation, section 314.94(a)(8)(iv) permits changes in order "to comply with current FDA labeling guidelines and guidance." 21 C.F.R. § 314.94(a)(8)(iv). Section 201.22(b) of the FDA's regulations requires that prescription drugs containing sulfites

shall bear the warning statement "Contains (insert the name of the sulfite, e.g., sodium metabisulfite), a sulfite that may cause allergic-type reactions . . . in certain susceptible people. The overall prevalence of sulfite sensitivity in the gen-

eral population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in non-asthmatic people."

21 C.F.R. § 201.22(b) (emphasis in the original). The FDA interpreted section 314.94(a)(8)(iv) to permit Gensia to include in its labeling the "warning statement" required by section 201.22, a current FDA labeling guideline. This interpretation is consistent with the language of section 314.94(a)(8)(iv). Furthermore, we see no merit to Zeneca's argument that the exception permitting revisions in labeling to comply with the FDA's current labeling guidelines only applies in situations in which the guidelines are issued after approval of the pioneer drug but before approval of the generic.

In sum, we conclude that the FDA's interpretation of 21 C.F.R. § 314.94(a)(8)(iv) to allow the label on Gensia's propofol with Sulfite to reflect a warning against possible allergic reaction to Sulfite contained in the drug is not plainly erroneous or inconsistent with the language of the regulation. Accordingly, the FDA's approval of Gensia's ANDA for propofol with Sulfite was not arbitrary and capricious for the second reason argued by Zeneca.

C

Finally, Zeneca argues that the FDA's approval of Gensia's propofol with Sulfite as a generic drug must be declared invalid and permanently enjoined because in determining that Gensia's propofol with Sulfite is safe the FDA relied upon safety evaluations that analyzed the wrong pH range. In this regard, Zeneca contends that the FDA conducted its safety evaluations of Gensia's propofol with Sulfite based on the initially proposed pH range of 6.0-7.5 rather than the lower pH range of 4.5-6.4 actually used in Gensia's ANDA for propofol with Sulfite.

In considering Zeneca's argument, we are mindful that the "FDA's judgments as to what is required to ascertain the safety and efficacy of drugs fall squarely within the ambit of the FDA's expertise and merit deference from us." A.L. Pharma, Inc. v. Shalala, 62 F.3d 1484, 1490 (D.C. Cir. 1995) (quoting Schering Corp. v. FDA, 51 F.3d 390, 399 (3d Cir. 1995)). Our review of the record reveals that Zene-

ca's argument, that the FDA relied upon the wrong pH range in determining that Gensia's propofol with Sulfite is safe, is without merit. Specifically, the record contains: (1) repeated references to the correct pH in Gensia's ANDA for propofol with Sulfite; (2) an agenda to a teleconference call between Gensia and FDA officials on the subject of the pH proposed in Gensia's ANDA for propofol with Sulfite; (3) the FDA's participation in the teleconference call held on August 19, 1998 to discuss the pH proposed in Gensia's ANDA for propofol with Sulfite; and (4) an assessment of the pH proposed in Gensia's ANDA for propofol with Sulfite and a determination by Dr. Mary Fanning, Associate Director of Medical Affairs for the OGD, that the proposed pH raised no safety issues. This evidence demonstrates that the FDA's safety determination regarding Gensia's propofol with Sulfite included its assessment of the actual lower pH range used in Gensia's final proposed version of propofol with Sulfite. **10**

### III

In sum, there is no basis in the record before us to hold that the FDA acted arbitrarily and capriciously in approving Gensia's ANDA for propofol with Sulfite. Accordingly, we affirm the district court's grant of Gensia's and the FDA's motions for summary judgment.

### AFFIRMED

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**10** We also note that the issue of Zeneca's standing was raised at oral argument. We conclude that Zeneca has standing. See Mova Pharm. Corp. v. Shalala, 140 F.3d 1060, 1074 (D.C. Cir. 1998) (noting that "numerous cases have found that a firm has constitutional standing to challenge a competitor's entry into its market"); Schering Corp., 51 F.3d at 395 (noting that FDA did not contest "that Schering's potential loss of monopoly profits upon FDA approval of a competitive generic substitute is sufficient to meet the Article III injury-in-fact standing requirement"); see also MD Pharm., Inc. v. DEA, 133 F.3d 8, 11 (D.C. Cir. 1998) ("We have previously held that 'increased competition represents a cognizable Article III injury,' Liquid Carbonic Industries Corp. v. FERC, 29 F.3d 697 (D.C. Cir. 1994), and MD's competitive injury is fairly traceable to DEA's decision to issue a certificate of registration to Mallinckrodt.").