

United States Court of Appeals

FOR THE DISTRICT OF COLUMBIA CIRCUIT

Argued December 3, 1997 Decided October 27, 1998

No. 97-5188

Serono Laboratories, Inc.,
Appellee

v.

Donna E. Shalala, et al.,
and
Ferring Pharmaceuticals Inc.,
Appellants

Consolidated with

No. 97-5227

Appeals from the United States District Court
for the District of Columbia
(No. 97cv01227)

Christine N. Kohl, Attorney, U.S. Department of Justice,
argued the cause for the federal appellants, with whom Frank

W. Hunger, Assistant Attorney General, Mary Lou Leary,
U.S. Attorney, and Douglas N. Letter, Litigation Counsel,
U.S. Department of Justice, were on the briefs.

John R. Fleder, David F. Weeda and Arthur Y. Tsien were
on the briefs for appellant Ferring Pharmaceuticals Inc.

Bruce S. Manheim, Jr. argued the cause for appellee, with
whom Terry S. Coleman and Matthew D. Peterson were on
the brief. Michael D. Petty entered an appearance.

Before: Henderson, Rogers and Garland, Circuit Judges.

Opinion for the Court filed by Circuit Judge Garland.

Garland, Circuit Judge: In this case we consider the validity of a district court order, preliminarily enjoining approval by the Food and Drug Administration ("FDA") of a generic drug, that was issued at the behest of the manufacturer of the competing brand-name drug. We previously stayed the preliminary injunction pending our resolution of this appeal. Because we find plaintiff has not satisfied the standards for a preliminary injunction, and in particular has not shown a likelihood of success on the merits, we now vacate the injunction.

I

The Food, Drug, and Cosmetic Act (the "Act") provides that "[n]o person shall introduce or deliver for introduction into interstate commerce any new drug" without first obtaining FDA approval. 21 U.S.C. s 355(a). To obtain FDA approval, the first applicant to market a drug, known as the "pioneer," must submit a new drug application ("NDA") containing, among other things, "full reports of investigations" made "to show whether or not such drug is safe for use and whether such drug is effective in use." Id. s 355(b)(1). Recognizing that the NDA process is costly and time-consuming, and seeking "to make available more low cost generic drugs," Congress amended the Act in 1984. H.R. Rep. No. 98-857, pt. 1, at 14 (1984), reprinted in 1984

U.S.C.C.A.N. 2647, 2647. The Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (known as the "Hatch-Waxman Amendments"), permits a manufacturer of a generic alternative to a pioneer drug to seek FDA approval by submitting an abbreviated new drug application ("ANDA") that need contain only the more limited information specified in 21 U.S.C. s 355(j)(2).¹

Two aspects of the ANDA process, corresponding to two kinds of drug ingredients, are relevant to this case. First, with respect to "active ingredients," the statute provides that the Secretary of Health and Human Services shall approve an application for a generic drug unless the Secretary finds, among other things, that "information submitted with the application is insufficient to show that the active ingredients are the same as the active ingredients of the listed [pioneer] drug...." 21 U.S.C. s 355(j)(3)(C)(ii). The FDA defines an "active ingredient" as "any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body...." 21 C.F.R. s 210.3(b)(7).

Second, with respect to "inactive ingredients," the statute provides that the Secretary shall approve an application unless she finds that "information submitted in the application or any other information available to the Secretary shows" that "the inactive ingredients of the drug are unsafe" or "the composition of the drug is unsafe ... because of the type or quantity of inactive ingredients included or the manner in which the inactive ingredients are included." 21 U.S.C. s 355(j)(3)(H). The FDA defines an "inactive ingredient" as

¹ Prior to the Hatch-Waxman Amendments, the FDA had established its own abbreviated procedures for generic copies of pioneer drugs approved before 1962, but not of pioneer drugs approved after 1962. The Amendments generally extended those procedures to cover generic copies of post-1962 pioneer drugs. See H.R. Rep. No. 98-857, pt. 1, at 14 (1984), reprinted in 1984 U.S.C.C.A.N. 2647, 2647; 130 Cong. Rec. 23,057 (1984) (statement of Rep. Waxman).

"any component other than an active ingredient." 21 C.F.R. s 210.3(b)(8).

In 1969, the FDA approved an NDA submitted by plaintiff Serono Laboratories, Inc. ("Serono") for Pergonal, a pioneer drug. Pergonal is a "menotropins" product administered by intramuscular injection and used to treat male and female infertility. A menotropins product is extracted from the urine of post-menopausal women, and contains two active ingredients: follicle-stimulating hormone ("FSH") and luteinizing hormone ("LH"). See Joint Appendix ("J.A.") 473; Dorland's Illustrated Medical Dictionary 1013 (28th ed. 1994). FSH and LH make up less than five percent of Pergonal, with lactose and uncharacterized urinary proteins ("UUPs") constituting the remainder. See FDA Br. at 6; Serono Br. at 4.

In 1990, Lederle Parenterals, Inc. ("Lederle") submitted an ANDA to the FDA seeking approval of a generic version of Pergonal, now known as Repronex. Defendant-intervenor Ferring Pharmaceuticals Inc. ("Ferring") acquired the rights to Lederle's ANDA while it was pending. In December 1992, Serono filed a "citizen petition," pursuant to 21 C.F.R. s 10.30, urging the FDA to withhold approval of the ANDA. Serono argued, among other things, that the UUPs in the proposed generic drug were "inactive ingredients" that differed from those in Pergonal and had not adequately been demonstrated to be safe. J.A. 465-69.

In a subsequent meeting, and in a supplemental filing on March 21, 1997, Serono also argued that the active ingredient FSH in the proposed generic drug was not, as required by statute, "the same as" the FSH in Pergonal because of differences in "isoforms" of the two products. Id. at 481. FSH is a protein-based hormone consisting of two protein chains in a backbone-like configuration, with carbohydrate side chains. Natural variation in the carbohydrate elements leads to different isoforms of the hormone. See id. at 482-83. Serono argued that this isoform variation in FSH rendered Repronex different from Pergonal, and hence ineligible for an ANDA. Id. at 481-82.

On January 30, 1997, the FDA approved the ANDA for Repronex. Id. at 459-60. The FDA gave Repronex an "AB" rating in its publication, Approved Drug Products with Therapeutic Equivalence Evaluations (known as the "Orange Book"), meaning that physicians and pharmacists could substitute Repronex for Pergonal. See FDA Br. at 7-8. In a memorandum to the administrative record filed on that date, Gordon Johnston, the Deputy Director of the FDA's Office of Generic Drugs, addressed another issue that had surfaced during the review--a difference in the concentration of the inactive ingredient lactose in Repronex and Pergonal. Johnston noted that although a 1992 regulation required an inactive ingredient in a generic drug to be in the same concentration as in the pioneer drug, that regulation was not in effect when the ANDA for Repronex was filed in 1990. Johnston concluded that since FDA policy was to review an application under the regulations in effect at the time of filing, the different lactose concentrations did not preclude ANDA approval. He also found that they posed no safety concerns. Id. at 457-58 (Memorandum to Record by G. Johnston, Jan. 30, 1997) (hereinafter "Johnston Memorandum").

On May 30, 1997, Serono sued the FDA in district court, raising many of the same issues contained in its still-pending citizen petition as well as the additional issue of the differing lactose concentrations. See Complaint WW 21-23. On June 13, 1997, Serono moved for a preliminary injunction rescinding the FDA's approval of Repronex, and Ferring intervened as a defendant.

On June 17, 1997, the FDA issued its final decision denying Serono's citizen petition. J.A. 472-86 (Letter from J. Woodcock to Serono, June 17, 1997) (hereinafter "Woodcock Letter"). Dr. Janet Woodcock, Director of the FDA's Center for Drug Evaluation and Research, rejected Serono's claim that the isoform variation in the active ingredient FSH meant that the FSH in Repronex was not the "same as" the FSH in Pergonal. Dr. Woodcock acknowledged the isoform variation, but concluded that it was not "clinically significant for the product's intended uses" and therefore did not preclude a "sameness" finding for purposes of 21 U.S.C. s 355(j). Id. at

484. Dr. Woodcock further concluded that the differing lactose concentrations in the two products, as well as the differing UUP profiles, did not affect the safety of Repronex. Id. at 480-81 & n.12. She also rejected the characterization of the UUPs as "inactive ingredients," classifying them instead as "impurities." Id. at 479-80.

On July 28, 1997, the district court granted Serono's motion for a preliminary injunction, barred the FDA "from approving the Ferring ANDA," and ordered it to "rescind immediately its designation of an 'AB' rating [for Repronex] in the Orange Book." *Serono Lab. v. Shalala*, 974 F. Supp. 29, 37 (D.D.C. 1997). The district court found that Serono was likely to prevail on the merits of its claims; that Serono would suffer irreparable injury if interim relief were not granted; and that both the balance of harms to Serono and Ferring, and the public interest, favored granting injunctive relief. See id. at 32-37.

II

A court considering a plaintiff's request for a preliminary injunction must examine whether: (1) there is a substantial likelihood plaintiff will succeed on the merits; (2) plaintiff will be irreparably injured if an injunction is not granted; (3) an injunction will substantially injure the other party; and (4) the public interest will be furthered by the injunction. See *Washington Metro. Area Transit Comm'n v. Holiday Tours, Inc.*, 559 F.2d 841, 843 (D.C. Cir. 1977). These factors interrelate on a sliding scale and must be balanced against each other. "If the arguments for one factor are particularly strong, an injunction may issue even if the arguments in other areas are rather weak." *CityFed Fin. Corp. v. Office of Thrift Supervision*, 58 F.3d 738, 746 (D.C. Cir. 1995); see *Holiday Tours*, 559 F.2d at 843-45.

We review the district court's weighing of the preliminary injunction factors under the "abuse of discretion" standard, see *Transohio Sav. Bank v. Director, Office of Thrift Supervision*, 967 F.2d 598, 614 (D.C. Cir. 1992), and its findings of fact under the "clearly erroneous" standard, see *National*

Wildlife Fed'n v. Burford, 835 F.2d 305, 319 (D.C. Cir. 1987). "[T]o the extent the district court's decision hinges on questions of law," however, "our review is 'essentially de novo.'" *O'Hara v. District No.1-PCD*, 56 F.3d 1514, 1522 (D.C. Cir. 1995) (quoting *Transohio*, 967 F.2d at 614).

III

Serono's argument that it is likely to succeed on the merits depends upon the validity of its contentions regarding three of Repronex's ingredients: FSH, lactose, and UUPs. We consider each of these in turn.

A

As noted above, FSH is an active ingredient in both Repronex and Pergonal. The Hatch-Waxman Amendments provide that the FDA "shall approve" an ANDA for a generic drug unless it finds, among other things, that the information submitted "is insufficient to show that the active ingredients are the same as the active ingredients of the listed drug." 21 U.S.C. s 355(j)(3)(C)(ii) (emphasis added). FDA regulations also state that "[f]or determining the suitability of an abbreviated new drug application, the term 'same as' means identical in active ingredient(s)...." 21 C.F.R. s 314.92(a)(1) (emphasis added).

As we also have noted, the chemical structure of FSH roughly consists of two components: (1) a protein backbone with a specific amino acid sequence, and (2) carbohydrate side chains. See J.A. 482-83 (Woodcock Letter). In concluding that the FSH in Repronex is the "same as" or "identical" to that in Pergonal, the FDA determined that their protein backbones and amino acid sequences are identical. Id. at 483. There are, however, slight natural variations in the configuration of the carbohydrate side chains, a phenomenon known as "microheterogeneity." See id. at 482-83. But, the FDA observed, "complete chemical identification of all the carbohydrate variants in a protein product often is not possible or feasible," id. at 482, a point Serono does not dispute. Indeed, it usually is not even possible "to assure by chemical analysis

that different batches" of the same product "are identical at the level of the carbohydrate side chains"--including different batches of Pergonal itself. Id. at 482-83.

In light of the fact that "most glycoprotein products will have microheterogeneity," the FDA determined that the relevant "question is how much variation should be permitted." Id. at 482. The agency answered that question as follows:

To be considered to have the same active ingredients as the reference listed drug, generic FSH products based on Pergonal as the reference listed drug must have the same primary structure, i.e., the same protein backbone and amino acid sequence as Pergonal (assured by using the same natural source material), the same potency, and the same degree of batch-to-batch uniformity. The batch-to-batch uniformity of Pergonal is achieved using in vivo rat potency tests, specified by the U.S. Pharmacopeia [USP].... The bioactivity of each batch of generic Menotropins ... is also controlled using USP rat bioassays, which provides the same assurance of potency and batch-to-batch uniformity as is provided by Serono for Pergonal.

Id. at 483. After reviewing additional clinical data, the FDA found "that any potential variations in FSH isoforms between the Ferring menotropins product and Pergonal appear not to be clinically significant for the product's intended uses." Id. at 484. The FDA concluded that such clinical identity ren-

ders menotropins products "the same for the purposes of 21 U.S.C. s 355(j)," *id.*, as long as the protein backbone, amino acid sequence, and potency are the same, and the degree of batch-to-batch variation in isoforms is no different than that in Pergonal itself, *id.* at 483.

Serono argues, and the district court agreed, that "same as" under the statute, and "identical" under the regulation, must mean absolute "chemical" identity. The court rejected the FDA's view that "clinical" identity is sufficient for a menotropins product as long as the above-described conditions are met, and therefore concluded that Serono was likely to prevail on the merits of its claim that the FSH in Repronex

and Pergonal is not the same. See *Serono Lab.*, 974 F. Supp. at 32-34. Since the district court's conclusion rests on issues of statutory and regulatory interpretation, we review that conclusion de novo.

Chevron U.S.A. Inc. v. Natural Resources Defense Council, Inc., 467 U.S. 837 (1984), governs our analysis of the validity of an agency's interpretation of a statute. Under *Chevron*, we first ask "whether Congress has directly spoken to the precise question at issue," in which case we "give effect to the unambiguously expressed intent of Congress." *Id.* at 842-43. But if Congress has been silent or ambiguous about the meaning of the specific question at issue, we defer to the agency's interpretation so long as it is "based on a permissible construction of the statute." *Id.* at 843.

In evaluating the first *Chevron* inquiry, we use "traditional tools of statutory construction" to determine whether Congress has unambiguously expressed its intent. *Id.* at 843 n.9. In this case, the statute does not define the term "same as," and does not indicate whether chemical or clinical identity was contemplated. We need to consider, therefore, what the terms mean in context. See *McCarthy v. Bronson*, 500 U.S. 136, 139 (1991). What the statute requires to be the "same" are the two drugs' "active ingredients," and FDA regulations pre-dating the Hatch-Waxman Amendments define an "active ingredient" as "any component that is intended to furnish a pharmacological activity or other direct effect." 21 C.F.R. s 210.3(b)(7) (1978). Hence, the ingredients that are to be compared for "sameness" are themselves defined in terms of pharmacological activity, adding credibility to the FDA's view that chemical identity is not the only way to read the statutory language.

The district court rejected this reading, in part because in its view, "[n]othing in [s 355(j)] permits an ANDA applicant to substitute USP animal assays for information demonstrating that the active ingredients of the proposed generic product are identical to those in the innovator product." *Serono Lab.*, 974 F. Supp. at 33. As noted above, the FDA permitted Ferring to use such assays to ensure the potency and batch-

to-batch uniformity of Pergonal. But while the court was correct in noting that nothing in the statute permits the use of animal assays, the important point is that nothing in the statute prohibits their use. Indeed, the statute says nothing at all about the type of information an applicant must submit to demonstrate "sameness," nor about the type of information upon which the FDA may rely. It says only that the information must not be "insufficient" to show that the active ingredients are the same. 21 U.S.C. s 355(j)(3)(C)(ii). If anything, this broad grant of discretion to the agency with respect to the information it may consider in making a finding of "sameness" indicates that Congress did not have one precise definition of the term in mind. Cf. Schering Corp. v. FDA, 51 F.3d 390, 399-400 (3d Cir. 1995) (holding that FDA's interpretation of 21 U.S.C. s 355(j)(7)(B) "as not limiting its discretion to determine what tests or studies would provide it with appropriate information from which to determine bioequivalence is a reasonable construction of the Act").

Moreover, the statutory phrase must be read in the context of the kind of drug at issue. As Dr. Woodcock noted, "it is usually not possible to assure by chemical analysis that different batches of [a protein product like FSH] are identical at the level of the carbohydrate side chains." J.A. 482. For the same reason, "batch to batch variability in isoform patterns" exist for Pergonal itself. Id. at 483. This means that if absolute chemical identity were required, it would not be possible to say any generic was the "same as" Pergonal, because the "batch to batch variability" would make the target of the comparison (not just Pergonal, but the specific batch of Pergonal) indeterminate. Indeed, the Woodcock Letter indicates that if absolute chemical identity were required, not only menotropins but other categories of protein products would be excluded from the ANDA process as well. See id. at 482; see also id. at 317 (internal FDA memorandum noting that other products derived from natural sources besides proteins, including lipids, phospholipids and oligosaccharides, also "can not be fully characterized chemically"). Yet, it seems likely--although by no means certain--that if Congress had intended to exclude entire categories of drugs

from the scope of the Hatch-Waxman Amendments, which were passed to "facilitat[e] the approval of generic copies of drugs," Mead Johnson Pharm. Group v. Bowen, 838 F.2d 1332, 1333 (D.C. Cir. 1988), there would be some mention of that fact in the statute or legislative history. Instead, both are wholly silent on the subject. We thus conclude that the statute does not unambiguously require the term "same as" to be defined as complete chemical identity.

Turning to the second Chevron inquiry, we ask whether the agency's definition is "based on a permissible construction of the statute," Chevron, 467 U.S. at 843, which requires only that its construction be a "reasonable" one, id. at 844. Similarly, we defer to an agency's reading of its own regulations,

here the regulation defining "same as" as "identical to," unless it is "plainly erroneous or inconsistent with the regulation." *Auer v. Robbins*, 117 S. Ct. 905, 911 (1997) (internal quotation omitted); *Cassell v. FCC*, No. 97-1005, slip op. at 10, 1998 WL 598099 at *6 (D.C. Cir. Sept. 11, 1998). We conclude that the FDA's definition of "same as" and "identical," as applied to menotropins products, is reasonable.

The FDA concluded that "[t]o be considered to have the same active ingredients as the reference listed drug, generic FSH products based on Pergonal ... must have the same primary structure, i.e., the same protein backbone and amino acid sequence as Pergonal (assured by using the same natural source material), the same potency, and the same degree of batch-to-batch uniformity." J.A. 483. The agency thus endeavored to guarantee the greatest degree of "sameness" possible for this kind of product, by ensuring an identical chemical structure where possible (in the primary structure), while reducing natural batch-to-batch variance (in the carbohydrate side chains) to the same degree as that found in the pioneer drug. To accomplish the latter, the FDA observed that Serono controls the batch-to-batch uniformity of Pergonal by using USP rat potency tests, and that Ferring does the same for Repronex. *Id.* at 483-84. The agency concluded that "it would be unreasonable to hold the generic menotropins product to a higher standard of uniformity than the standard used for Pergonal." *Id.* at 484 n.17.

Finally, Dr. Woodcock noted that there also were isoform variations between Pergonal and another approved menotropins product, Humegon, and that clinical trials and published literature on those two drugs "demonstrated no differences in safety and efficacy." *Id.* at 483. Those studies, the FDA found, indicate that "any currently observed differences in FSH isoforms do not have clinical significance." *Id.* at 484. In light of the standards it set, and the evidence of clinical equivalence, Dr. Woodcock concluded that "the active ingredients, FSH and LH, of the approved menotropins products are the same for purposes of 21 U.S.C. s 355(j)." *Id.* (emphasis added).

The FDA's determination of what is required to establish "sameness" for purposes of the Act rests on the "agency's evaluations of scientific data within its area of expertise," and hence is entitled to a "high level of deference" from this court. *A.L. Pharma, Inc. v. Shalala*, 62 F.3d 1484, 1490 (D.C. Cir. 1995); see *Schering Corp.*, 51 F.3d at 399-400. The district court appeared to grant the FDA's determination less than this usual deference because internal FDA memoranda indicated there was some disagreement among FDA chemists as to whether the isoform variation rendered the active ingredients different. See *Serono Lab.*, 974 F. Supp. at 33 & n.6.2 But Chevron deference is owed to the decisionmaker authorized to speak on behalf of the agency, not to each individual agency employee. See *Michigan Citizens For An Indep. Press v. Thornburgh*, 868 F.2d 1285, 1293 (D.C. Cir. 1989) (giving Chevron deference to Attorney General's statutory interpretation over contrary view of Antitrust Division, be-

2 The district court also read the minutes of a 1993 meeting between FDA staff and Lederle (the original ANDA applicant) to indicate that the staff "implicitly" rejected the use of "the USP bioassay for menotropins" as a method for evaluating "pharmaceutical equivalence"--because the staff required Lederle to do additional chemical testing. *Serono Lab.*, 974 F. Supp. at 33 n.7. Whether or not this was the implication of the staff's actions, the views of FDA staff do not bind the agency's final decisionmaker. See 21 C.F.R. s 10.65(a) (action at meetings with FDA staff does not constitute final administrative action).

cause Congress "place[d] responsibility for reconciling the conflicting policies and values called for in this type of case [not] upon the Antitrust Division, but rather on the Attorney General"); cf. *San Luis Obispo Mothers For Peace v. United States Nuclear Regulatory Comm'n*, 789 F.2d 26, 33 (D.C. Cir. 1986) (en banc) (holding that the "position of an agency's staff, taken before the agency itself decided the point, does not invalidate the agency's subsequent application and interpretation of its own regulation"); *Homemakers N. Shore, Inc. v. Bowen*, 832 F.2d 408, 413 (7th Cir. 1987) (" 'The Secretary's position' is the position of the Department as an entity, and the fact that people in the chain of command have expressed divergent views does not diminish the effect of the agency's resolution of those disputes."). Indeed, were we to hold otherwise, we would effectively empower any individual em-

ployee not just to veto the views of the agency head, but to preclude any deference to the agency at all, since we would have no basis for deciding to whose view we should defer. Dr. Woodcock was the authorized decisionmaker for the agency on this matter, see 21 C.F.R. s 5.31(a)(2)(i) (Director of Center for Drug Evaluation and Research authorized to grant or deny citizen petition), and hers is the view to which the courts owe deference.

Of course, differing views among an agency's staff may indicate that there is more than one reasonable way to read a statute. And there may well be more than one reasonable way to read this one. But under Chevron, courts are bound to uphold an agency interpretation as long as it is reasonable--regardless whether there may be other reasonable, or even more reasonable, views. Here, the FDA interpreted "same as," in the context of menotropins products, to require: clinical equivalence to the pioneer, chemical identity to the extent possible, and limitations on inherent isoform variation to the same extent as in the pioneer. This interpretation is a reasonable, and hence permissible, reading of the statutory term. Cf. Bristol-Myers Squibb Co. v. Shalala, 91 F.3d 1493, 1499-1500 (D.C. Cir. 1996) (upholding FDA determination that statutory provision requiring that labeling of generic be

the "same as" labeling of pioneer, permitted FDA to approve a generic even though its label would not include all of the indications on the label of the pioneer). It is also a reasonable interpretation of the word "identical" in the agency's own regulation.³

We conclude that the district court erred as a matter of law in ruling that the FDA's interpretation of the statute and regulations was impermissible. As that ruling was the principal basis for the court's conclusion that Serono was likely to succeed on the merits of its claim that the active ingredient FSH in Repronex was not the "same as" that in Pergonal, the court erred in that conclusion as well.

³ The Federal Register notice accompanying 21 C.F.R. s 314.92(a)(1), which defines the term "same as" to mean "identical," supports the FDA's view that the regulation does not require complete chemical identity regardless of the kind of drug at issue. The notice indicates the FDA decided against adopting a proposal that would have required "applicants to demonstrate that their active ingredients 'exhibit the same physical and chemical characteristics[;] that no additional residues or impurities can result from the different manufacture or synthesis process; and that the stereochemistry characteristics and solid state forms of the drug have not been altered.'" 57 Fed. Reg. 17,950, 17,958-59 (1992). Instead, the notice indicates the FDA adopted a more flexible approach:

FDA will consider an active ingredient to be the same as that of the reference listed drug if it meets the same standards for identity. In most cases, these standards are described in the U.S. Pharmacopeia [USP]. However, in some cases, FDA may prescribe additional standards that are material to the ingredient's sameness. For example, for some drug products, standards for crystalline structure or stereoisomeric mixture may be required. Should questions arise, an applicant should contact the Office of Generic Drugs to determine what information would be necessary to demonstrate that its active ingredient is the same as that in the reference listed drug.

Id. at 17,959 (emphasis added). As discussed in the text above, the FDA followed this approach here, "rely[ing] on the USP test for its determination of the sameness of the active ingredients" in Repronex and Pergonal. J.A. 483 (Woodcock Letter).

B

Lactose is an inactive ingredient in both Repronex and Pergonal. With regard to inactive ingredients, the Act directs the FDA to approve an ANDA for a generic drug unless the agency finds the inactive ingredients are "unsafe for use" or the composition of the drug is unsafe "because of the type or quantity" of the inactive ingredients. 21 U.S.C. s 355(j)(3)(H). Although the statute itself contains no other limitation, an FDA regulation that became effective in 1992 provides that the agency will not grant an ANDA for a generic drug intended for parenteral (injectable) use, "unless it contains the same inactive ingredients ... in the same

concentration as the listed drug...." 21 C.F.R. s 314.127(a)(8)(ii)(B). Repronex is intended for parenteral use and, although there is no dispute that the lactose in Repronex and Pergonal is the same, it is conceded that the concentration of lactose in the two drugs is different. Repronex contains twice as many milligrams of lactose per vial as Pergonal. See J.A. 457.

Deputy Director Johnston addressed this issue in his January 1997 memorandum, determining that because the ANDA for Repronex was filed in 1990, the regulations that were in effect in that year rather than those that went into effect in 1992 should apply. He explained his determination as follows:

OGD [the Office of Generic Drugs] has generally used the filing and approval criteria in effect at the time of submission as the basis for approval of applications. At the time that [the Repronex] applications were submitted in June 1990, the regulations implementing the Waxman-Hatch amendments were not in effect. The regulations in effect at that time did not require that parenteral products contain the same inactive ingredients at the same concentration. [See, e.g., 21 C.F.R. ss 314.125(b)(2), (3), (4) (1990); 21 C.F.R. s 314.2 (1984).] Moreover, OGD did not have a specific policy that addressed limitations on inactive ingredients in parenteral products. Thus, with regard to inactive ingredients, the generic menotropins application was approvable

under the regulations in effect at the time the application was submitted.

J.A. 457.

The district court rejected Johnston's determination. The court did not dispute the FDA's representation that its policy has been to apply the regulations in effect at the time of the submission of the ANDA. See, e.g., 48 Fed. Reg. 2751, 2753 (1983) (in pre-Hatch-Waxman period, applying regulations only to ANDAs submitted after the regulations' effective date). Instead, it pronounced itself "dumbfound[ed]" by the contention that a new drug could "come to market on a more lenient basis than required by existing law." *Serono Lab.*, 974 F. Supp. at 34-35. "While the court understands Grandfather clauses," it said, "if one does exist in this case, they have no place where the public safety is involved." *Id.* at 35.

We do not find the FDA's policy so dumbfounding. First, the agency's decision not to apply the 1992 "same concentration" rule did not free the agency to disregard safety considerations. The statute's bottom line--that the agency must be satisfied that the lactose in the generic is not unsafe--still holds. Second, as long as the agency continues to ensure an ingredient's safety on a case-by-case basis, the decision not to retroactively apply a per se rule regarding concentration is not irrational. The application process for new drugs can be a long one--even the "abbreviated" ANDA process utilized here took more than six years for an agency decision. If

every pending application had to be revised each time the FDA changed its regulations, the process would become much more lengthy--even Sisyphean if the rules of the game changed each time the application neared the finish line. Indeed, if complete retroactivity were required, the unintended consequence might well be to force the agency to limit its revision of regulations, in order to prevent the process from becoming unworkable.

More important, however we or the district court may appraise the reasonableness of grandfather clauses in drug regulation, Congress itself plainly contemplated that the FDA would follow a grandfather policy. Although the Hatch-

Waxman Amendments authorized the FDA to promulgate regulations to implement its new ANDA provisions, and one such regulation was the 1992 "same concentration" rule, the Amendments also expressly stated that ANDAs "may be submitted in accordance with" the FDA's existing regulations until the new regulations "take effect." Pub. L. No. 98-417, s 105(b), 98 Stat. 1585, 1597 (codified at 21 U.S.C. s 355 note). As the FDA rightly points out, for this provision to have any meaning, the FDA must also be permitted to review applications under the regulations in effect at the time of the submission. Accordingly, the district court erred as a matter of law in concluding that Serono was likely to succeed on the merits because the FDA had failed to apply its 1992 regulation to the Repronex ANDA.⁴

The district court further stated that even if the FDA did not have to apply the 1992 regulation, the court nonetheless was "uncertain" whether the bottom-line requirement that the lactose in Repronex not be "unsafe" was satisfied. Serono Lab., 974 F. Supp. at 35. The court's uncertainty derived, it said, from the following sentence in the Johnston Memorandum: "'[T]he difference in the amount of lactose present in [Repronex] does not raise serious questions of safety.'" Id. (citing J.A. 458 (Johnston Memorandum)) (emphasis added by district court). The agency's use of the word "serious," the district court suggested, indicated too much "tentativeness" to give the court comfort. Id.

The FDA contends, and we agree, that the district court misread the memorandum. Presumably the court thought the use of the adjective "serious" indicated the FDA still might harbor questions, even if not serious ones. In context, however, it is apparent that Deputy Director Johnston did not use "serious" to suggest that unresolved questions remained. Rather, he used serious as a synonym for "reasonable." This

⁴ Serono's citations to cases regarding an agency's duty to comply with its own regulations are inapposite. The FDA did not "fail to comply" with an applicable regulation. Rather, it found that under its existing policy, the 1992 regulation was inapplicable to the earlier-filed ANDA for Repronex.

usage is made clear by the language Johnston used to summarize his analysis of the safety issue: "[T]here is no reasonable basis to conclude that the lactose would have been or is a safety concern." J.A. 458 (emphasis added); see also id. at 481 n.12 (Woodcock Letter) ("[T]he lactose concentration variation between Ferring's product and Serono's product does not pose safety concerns.").⁵

Nor does anything in the Johnston Memorandum suggest the FDA reached its conclusion cavalierly. Deputy Director Johnston made clear that although the Repronex ANDA was not subject to the "same concentration" regulation, the agency had "assured that safety was not a problem." Id. at 458. There was "no reasonable basis" for a safety concern arising from the different concentrations of lactose, he said, for four

reasons. First, "lactose is a sugar obtained from milk" which is commonly used as an inactive ingredient in many parenteral drug products, and which "has been found to be generally recognized as safe (GRAS) in preclinical or animal studies by the Center for Drug Evaluation and Research (CDER)." Id. Second, "lactose has been used safely in amounts that far exceed[] the amount present in [Repronex]." Id. Third, "every lot of [Repronex] is checked for efficacy by [a recognized] method." Id. And finally, "three safety studies were performed on the product that showed no demonstrated potential for an increase in the incidence and severity of cardiovascular incidents or hypersensitivity and anaphylactic reactions." Id.

Nothing in the Johnston Memorandum, then, suggests the agency was left with any residual safety concerns. To the contrary, Deputy Director Johnston concluded: "Thus, FDA determines that there is not [a] safety concern (from the

⁵ Johnston's use of the word "serious" appears to have been nothing more than a parroting of the language in the FDA regulation cited by Serono in its citizen petition. See J.A. 465 ("An inactive ingredient ... will be considered unsafe if there is a reasonable basis to conclude that the ingredient ... raises serious questions of safety.") (emphasis added) (citing 21 C.F.R. s 314.127(a)(8)(ii)(A)).

inactive ingredients or the impurity profile), efficacy concern, or bioequivalence problem that would preclude approval of the generic drug product." *Id.* To the extent the district court concluded otherwise regarding the firmness of the FDA's view, that conclusion was clearly erroneous.

Serono contends that however certain the agency may have been about the safety of the lactose in Repronex, the district court's decision was still justified because the three safety studies referred to in the Johnston Memorandum were animal studies. According to Serono, the Hatch-Waxman Amendments prohibit the use of such studies to analyze safety. The district court did not explicitly rely on this argument, but Serono presses it as an alternate ground for affirmance. *Serono Br.* at 33-35.

The only provision of the Act to which Serono points for support of its no-animal-studies proposition is one that states the FDA "may not require that an abbreviated application contain information in addition to that required by clauses (i) through (viii)" of 21 U.S.C. s 355(j)(2)(A). *Id.* Because nothing in those clauses mentions animal studies, Serono contends they are barred. This provision, however, does not bear the weight Serono applies.

First, the indicated clauses do not suggest that animal studies are in any way disfavored. The clauses simply describe what the "information" in an application must "show." They do not specify the kinds of studies that can or cannot be used to satisfy the requirement. See, e.g., *id.* s 355(j)(2)(A)(ii)(II) ("An abbreviated application for a new drug shall contain ... information to show that the active ingredients of the new drug are the same as those of the listed drug.").

Moreover, the most the provision cited by Serono does is bar the FDA from requiring an applicant to submit more information than required by the statute. It does not bar an applicant from voluntarily submitting additional information--including animal studies--as part of its ANDA. Nor does it bar the FDA from relying on animal studies to make its findings. To the contrary, the statute expressly provides

that the FDA may make safety determinations on the basis of information submitted in the ANDA "or any other information available to the Secretary." *Id.* s 355(j)(3)(H). Accordingly, we reject Serono's contention that the Act prohibits reliance on animal studies to confirm the safety of Repronex's inactive ingredients. See *Schering Corp.*, 51 F.3d at 399 (holding that 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").⁶

In sum, we conclude the district court erred in finding that Serono was likely to succeed on the merits regarding its lactose claim, because that finding was based on (1) the legally erroneous conclusion that the FDA was bound to

apply its 1992 "same concentration" regulation to Repronex's 1990 ANDA, and (2) the clearly erroneous factual finding that the agency was "tentative" in its views regarding Repronex's safety. Serono's alternative rationale, that the FDA unlawfully employed animal studies in this case, also fails.

C

Finally, Serono argues that the conceded differences in the UUPs in Repronex and Pergonal render the former unfit for ANDA approval. Serono regards the UUPs as inactive ingredients, and again cites the FDA's 1992 regulation, which

6 We also reject Serono's contention that FDA policy bars the agency's use of animal studies in the manner in which they were used here. Serono relies on a Federal Register notice stating that an ANDA is not an appropriate vehicle for approval of a drug if animal or clinical studies are "necessary to show that the drug is safe or effective." 57 Fed. Reg. at 17,958. The notice explains, however, that such studies are permitted if they constitute "limited confirmatory testing," i.e., "simple studies [that are] intended to rule out unlikely problems" and that are not "necessary" to demonstrate overall safety. *Id.* The FDA's determination that the animal studies at issue here fall within that category is supported by the fact that the studies were only one of four grounds upon which the agency relied for its conclusion that the lactose in Repronex is safe. See J.A. 458.

requires that an ANDA not be approved unless the generic drug "contains the same inactive ingredients ... in the same concentration as the listed drug...." 21 C.F.R. s 314.127(a)(8)(ii)(B). The district court relied heavily on what it characterized as the FDA's "efforts to skirt" this regulation in concluding that Serono was likely to succeed on the merits of this claim. See *Serono Lab.*, 974 F. Supp. at 34.

As we have already held, however, the FDA appropriately declined to apply its 1992 regulation to Ferring's 1990 ANDA, leaving only the statutory (and similar 1990 regulatory) requirement that available information not show the generic drug's inactive ingredients are "unsafe." 21 U.S.C. s 355(j)(3)(H). The Woodcock Letter adequately addressed that requirement. Dr. Woodcock noted that Ferring "performed three confirmatory safety studies to rule out the unlikely possibility [asserted in Serono's citizen petition] that the differences in impurity profiles between the Ferring and Serono products might affect the safety of the generic drug product." J.A. 480. Although the studies involved animals, we have held above that the statute does not bar FDA from relying on such studies for this purpose. Moreover, Woodcock further determined that the results of the animal studies were "consistent with human clinical studies" submitted by another menotropins manufacturer, Organon, in support of its NDA for another menotropins product, Humegon, which "like Ferring's product, contains urinary proteins that may be different from Pergonal." *Id.* at 481. After reviewing those studies, Woodcock concluded that "Ferring has adequately

demonstrated that the potential difference (from Pergonal) in urinary proteins is not a safety concern." Id. Both this court and the district court are bound to show deference to the agency's fact-finding in this area of its technical expertise. See, e.g., Schering Corp., 51 F.3d at 399.

Serono interposes one final argument. It contends we should ignore the Woodcock Letter because it was a post hoc rationalization of the agency's action. Although the letter was the agency's response to Serono's citizen petition, Serono labels it post hoc because it was issued after Serono had already moved for injunctive relief in the district court. In

this case, however, timing isn't everything. Dr. Woodcock's letter represents the considered views of the agency-decisionmaker herself, announced at the usual point in the agency's decision-making process (the end), rather than the views of litigation counsel trying to come up with an explanation after the fact. See *Auer*, 117 S. Ct. at 912 ("There is simply no reason to suspect that the interpretation does not reflect the agency's fair and considered judgment on the matter in question."). The fact that Serono filed for preliminary injunctive relief before the agency ruled on its petition does not change the analysis. Cf. *Local 814, Int'l Bhd. of Teamsters v. NLRB*, 546 F.2d 989, 992 (D.C. Cir. 1976) (" 'The post hoc rationalization' rule is not a time barrier which freezes an agency's exercise of its judgment after an initial decision has been made and bars it from further articulation of its reasoning. It is a rule directed at reviewing courts which forbids judges to uphold agency action on the basis of rationales offered by anyone other than the proper decisionmakers.").

In sum, the district court's conclusion that Serono was likely to succeed on the merits of this claim was substantially based on its determination that the law compelled the FDA to apply its 1992 regulation requiring that the inactive ingredients in a generic drug be the same as those in the pioneer. That determination was legally erroneous. On the other hand, the record indicates that the FDA's treatment of the UUPs is likely to satisfy the statutory safety requirement for inactive ingredients. See J.A. 480-81 (evaluating safety of UUPs as if they were inactive ingredients). Accordingly, we need not consider the FDA's alternative argument that the UUPs are not "inactive ingredients" at all, but rather are merely "impurities" not subject to that requirement. See *id.* at 479-80.

IV

In this case, our conclusion that Serono is not likely to succeed on the merits effectively decides the preliminary injunction issue. Here, the other preliminary injunction fac-

tors--injury to Serono, injury to Ferring, and the public interest--either are a wash or are inextricably linked to the merits.

Serono contends that it will be irreparably injured if the FDA is not enjoined from approving Repronex, because it will suffer an unrecoverable loss of sales to Ferring. But even if such a loss does constitute irreparable injury, as the district court found and defendants dispute, see *Serono Lab.*, 974 F. Supp. at 35, that injury must be weighed against the next factor--the extent to which an injunction will substantially injure the other party, Ferring. And that balance of harms results roughly in a draw. Whatever sales Serono will lose to Ferring in the absence of an injunction, Ferring will lose to Serono in the presence of one. See *Serono Lab. v. Shalala*, Civ. No. 97-1227 (D.D.C. Aug. 19, 1997) (J.A. 622) (district court order denying Ferring motion for stay pending appeal, because "while Ferring may be harmed by the granting of the preliminary injunction, Plaintiff would be equally harmed if the injunction were to be stayed"). As a consequence, even Serono concedes that the court should "ignore[] the injury to both companies when balancing the harms since the lost revenues at issue are offsetting." *Serono Br.* at 39-40;7 see *Delaware & Hudson Ry. Co. v. United Transp. Union*, 450 F.2d 603, 620 (D.C. Cir. 1971) ("It often happens that ... one party or the other will be injured whichever course is taken. A sound disposition ... must [then] depend on a reflective and attentive appraisal as to the outcome on the merits.").

The final preliminary injunction factor, the public interest, also offers Serono no support because it is inextricably linked with the merits of the case. If, as we have held, Serono is not likely to establish that Ferring's ANDA was wrongly approved, then public interest considerations weigh against an injunction. The purpose of the Hatch-Waxman Amendments was, after all, "to increase competition in the drug industry by facilitating the approval of generic copies of drugs." *Mead*

7 Because Ferring plans to sell Repronex for less than Serono sells Pergonal, whether the lost revenues are exactly offsetting depends upon the elasticity of demand.

Johnson, 838 F.2d at 1333. Congress expected that competition "to make available more low cost generic drugs." H.R. Rep. No. 98-857, pt. 1, at 14 (1984), reprinted in 1984 U.S.C.C.A.N. 2647, 2647. Congress' purpose is directly implicated here, the FDA argues, because Ferring has priced Repronex to sell at 40% below the price of Pergonal, and because there has been a shortage of this type of fertility drug. *FDA Br.* at 46 (citing J.A. 123, 133, 420, 458). As Deputy Director Johnston put it, "the availability of a generic menotropins injection ... will enable some patients to afford the drug product that previously could not." J.A. 458.8

Of course if the ANDA should not have been granted in this case, because the statute's standards--particularly its safety standards--were not met, then the public interest

balance plainly would weigh in favor of an injunction. But on the current record it appears likely that the ANDA was properly granted, and the FDA has assured this court, in the strongest possible terms, that there are no safety concerns. See FDA Br. at 46; Oral Arg. Tr. at 34. Neither we, nor the district judge, are scientists independently capable of assessing the validity of the agency's determination--beyond holding it to the standards of rationality required by the Administrative Procedure Act, 5 U.S.C. s 706(2)(A). See *Troy Corp. v. Browner*, 120 F.2d 277, 283 (D.C. Cir. 1997); *Schering Corp.*, 51 F.3d at 399. Indeed, not even Serono argues that the evidence shows Repronex represents a safety concern. At oral argument, Serono's counsel, choosing his words carefully, would say no more than that "we don't know whether there are unresolved safety issues." Oral Arg. Tr. at 22. Such agnosticism is too insubstantial a basis for us to rescind the decision of the expert agency entrusted by Congress with the authority to assess the safety of drugs.

8 For this reason, one of the public interest considerations relied upon by the district court--that "the reproductive potential of each woman declines with age ... and any lost cycle (usually of a month's duration) will contribute to the loss of reproductive potential"--cuts against rather than in favor of an injunction. *Serono Lab.*, 974 F. Supp. at 36.

v

For the foregoing reasons, we vacate the preliminary injunction entered by the district court and remand the case for further proceedings consistent with this opinion. Our opinion does not foreclose the possibility that at a trial on the merits, and upon a fuller record, Serono may be able to establish that there are grounds for overturning the grant of Repronex's ANDA. We hold only that upon the current record, Serono has failed to establish that it meets the criteria for the grant of a preliminary injunction.