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**BERLEX LABORATORIES, INC., Plaintiff, v. FOOD AND DRUG  
ADMINISTRATION, et al., Defendants.**

**Civil Action No. 96-0971 (JR)**

**UNITED STATES DISTRICT COURT FOR THE DISTRICT OF COLUMBIA**

*942 F. Supp. 19; 1996 U.S. Dist. LEXIS 15169*

**October 7, 1996, Decided  
October 7, 1996, FILED**

**DISPOSITION:** [\*\*1] Plaintiff's motion for summary judgment [# 48] DENIED. Defendants' motions to dismiss [# 36, # 39] treated as motions for summary judgment GRANTED and case DISMISSED.

**CASE SUMMARY:**

**PROCEDURAL POSTURE:** Plaintiff drug manufacturer filed a motion for summary judgment in its action against defendant United States Food and Drug Administration (FDA) and intervenor competitor drug manufacturer (competitor). The drug manufacturer sought a judgment declaring that the FDA's approval of the competitor's interferon beta product was unlawful and an order rescinding its approval. The FDA and the competitor filed cross-motions for summary judgment.

**OVERVIEW:** The drug manufacture was given market exclusivity of its drug under the Orphan Drug Act (Act), 21 U.S.C.S. § 360aa-360dd. When the FDA approved the competitor's similar drug, the drug manufacturer sought rescission of its action. The competitor intervened and all parties filed motions for summary judgment. The court on review granted the cross-motions of the FDA and the competitor. Giving deference to the FDA's interpretation of its regulations, the court held that the FDA had an adequate basis upon which to consider the competitor's drug "clinically superior" to the drug manufacturer's version when it relied exclusively on a single side effect. Accordingly, it did not act arbitrarily in nullifying the drug manufacturer's orphan drug protection. The drug manufacturer had standing to complain under the Public Health Service Act (PHSA), 42 U.S.C.S. § 262, of the approval. The record contained

ample support for FDA's comparability determination and for its finding that the competitor's drug was "safe, pure and potent" as required by the PHSA. As the FDA's comparability guidance document was interpretive and not legislative, its issuance did not require notice-and-comment rulemaking.

**OUTCOME:** The court denied the drug manufacturer's motion for summary judgment in its action to rescind the FDA's approval of a similar drug manufactured by a competitor. The court granted the cross-motions for summary judgment by the FDA and the competitor that the FDA's actions were not arbitrary, capricious, or unlawful.

**LexisNexis (TM) HEADNOTES - Core Concepts:**

*Administrative Law > Informal Agency  
Actions Governments > Agriculture & Food > Federal  
Food, Drug & Cosmetic Act*

[HN1] The Orphan Drug Act, 21 U.S.C.S. § 360aa-360dd, permits Food and Drug Administration (FDA) approval of a drug that treats the same condition as did an original orphan drug if the FDA determines that the two drugs are not the same. A new drug is not considered the same as a previously approved drug if the new drug is "clinically superior." 21 C.F.R. § 316.3(b)(13)(ii). A new drug is "clinically superior" if it offers greater safety in a substantial portion of the target populations. 21 C.F.R. § 316.3(b)(3)(ii).

*Governments > Agriculture & Food > Federal Food,  
Drug & Cosmetic Act*

[HN2] 21 U.S.C.S. § 360bb(2) provides that "orphan drugs" are drugs that treat diseases 1) affecting fewer than 200,000 persons or 2) affecting more than 200,000 person for which there is no reasonable expectation that the cost of developing and marketing the drug will be recovered from sales in the United States.

**Administrative Law > Informal Agency Actions Governments > Agriculture & Food > Federal Food, Drug & Cosmetic Act**

[HN3] Under Food and Drug Administration (FDA) regulations, an example of "greater safety" in a substantial portion of a target population is the elimination of an ingredient or contaminant that is associated with relatively frequent adverse effects. 21 C.F.R. § 316.3(b)(3)(ii). Even a small demonstrated diminution in adverse reactions is sufficient to allow a finding of clinical superiority of a new drug over an original orphan drug.

**Administrative Law > Judicial Review > Reviewability > Preclusion Administrative Law > Agency Rulemaking > Rule Application & Interpretation**

[HN4] The court gives deference to the Food and Drug Administration's (FDA) interpretation of its regulations. The FDA's application of an interpretation in a specific case is upheld if the agency has based its decision upon relevant factors that have evidentiary support.

**Administrative Law > Judicial Review > Standing**

[HN5] Prudential standing to challenge an agency decision exists if the challenger is within the zone of interest to be protected or regulated by the statute. A plaintiff has no right to bring suit against an agency, however, if the plaintiff's interests are so marginally related to or inconsistent with the purposes implicit in the statute that it cannot reasonably be assumed that Congress intended to permit the suit.

**Administrative Law > Judicial Review > Standing**

[HN6] A plaintiff who has a competitive interest in confining a regulated industry within certain congressionally imposed limitations may sue to prevent the alleged loosening of those restrictions, even if the plaintiff's interest is not precisely the one that Congress sought to protect.

**Administrative Law > Judicial Review > Standing**

[HN7] The manufacturer of a "pioneer" drug has standing to sue the Food and Drug Administration (FDA) under the Public Health Service Act, 42 U.S.C.S. § 262, for its alleged failure to enforce safety and efficacy standards against a competitor. The interests of the plaintiff and the FDA are "systematically aligned" in such a way as to promote the principal safety objective

of the statute and the manufacturer is thus a "suitable challenger" for standing purposes. The pioneer drug manufacturer is well-positioned to monitor the FDA regulations implementing statutorily mandated requirements when it is their pioneer drug the generic manufacturer seeks to copy. The economic interest of such a plaintiff provides an incentive for the plaintiff to advocate the overriding necessity of ensuring public access to safe commercial drugs.

**Administrative Law > Agency Rulemaking > Formal Rulemaking Administrative Law > Informal Agency Actions Governments > Agriculture & Food > Federal Food, Drug & Cosmetic Act Administrative Law > Agency Rulemaking > Rule Application & Interpretation**

[HN8] 42 U.S.C.S. § 262(d)(1) of the Public Health Service Act, 42 U.S.C.S. § 262, authorizes the Food and Drug Administration (FDA) to license biological products that meet standards designed to insure the continued safety, purity, and potency of such products. The FDA's regulations require applicants for licenses to submit data derived from nonclinical laboratory and clinical studies which demonstrate that the manufactured product meets prescribed standards of safety, purity, and potency. 21 C.F.R. § 601.2(a). While no quantitative or measurable "standards" for safety, purity or potency exist, the regulations set out definitions of those terms that guide FDA's case-by-case determinations. 21 C.F.R. § 600.3.

**Administrative Law > Judicial Review > Reviewability > Preclusion Administrative Law > Agency Rulemaking > Rule Application & Interpretation**

[HN9] The Food and Drug Administration's (FDA) policies and its interpretation of its own regulations are paid special deference because of the breadth of Congress' delegation of authority to FDA and because of FDA's scientific expertise.

**Administrative Law > Agency Rulemaking > Informal Rulemaking**

[HN10] The Administrative Procedure Act requires notice-and-comment rulemaking when an agency issues new "legislative" or "substantive" rules that establish binding norms having the force of law. 5 U.S.C.S. § 553. "Interpretive" rules, however, are expressly excused from the notice-and-comment requirements. 5 U.S.C.S. § 553(b)(3)(A). An interpretive rule is one issued by an agency to advise the public of the agency's construction of the statutes and rules which it administers. A rule is legislative, rather than interpretive, if any one of the following four questions is answered in the affirmative: (1) whether in the absence of the rule there would not be an adequate legislative basis for agency action to confer

benefits or ensure the performance of duties; (2) whether the agency has published the rule in the Code of Federal Regulations; (3) whether the agency has explicitly invoked its general legislative authority; or (4) whether the rule effectively amends a prior legislative rule.

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**JUDGES:** James Robertson, United States District Judge

**OPINIONBY:** James Robertson

**OPINION:**

**[\*21] MEMORANDUM OPINION**

Plaintiff Berlex Laboratories, Inc. ("Berlex") manufactures Betaseron, a biological drug classified as an interferon beta product. n1 On July 23, 1993, the Food and Drug Administration approved Betaseron for the treatment of multiple sclerosis. Because it was the first interferon **[\*\*2]** beta product approved for the treatment of MS, Betaseron was also given market exclusivity for seven years under the Orphan Drug Act. 21 U.S.C. § § 360aa-360dd.

n1 Interferons are a family of proteins in the human body that inhibit the replication of a wide spectrum of viruses and are important in the functioning of the body's immune system. The interferon beta products discussed in this opinion are produced by modifying and recombining portions of deoxyribonucleic acid (DNA) molecules and inserting the altered molecules into other cells.

Intervenor-defendant Biogen, Inc. developed an interferon beta product similar to Betaseron. On May 17, 1996, the FDA approved Biogen's product, known as

Avonex, for manufacture and sale in the United States for the treatment of MS.

In this action, Berlex seeks a judgment declaring that FDA's approval of Biogen's Avonex was unlawful and an order rescinding that approval. Berlex's claims are that FDA 1) unlawfully nullified Betaseron's Orphan Drug protection upon an arbitrary **[\*\*3]** and capricious finding that Avonex is "clinically superior" to Betaseron; 2) violated the Public Health Service Act, 42 U.S.C. § 262, and regulations issued thereunder by approving **[\*22]** Avonex without requiring the completion of full clinical trials; and 3) failed to conduct required notice-and-comment rulemaking before issuing a "comparability guidance document" that was important to the approval of Avonex.

Biogen has intervened as a defendant. Cross-motions for summary judgment were argued on September 5, 1996. This memorandum sets forth the reasons for the accompanying order granting the motions of FDA and Biogen and denying the motion of Berlex.

**BACKGROUND**

FDA's approval of Avonex on May 17, 1996, marked the first time FDA had approved a biological product for manufacture and sale without requiring the completion of full clinical trials on that actual product. In approving Avonex, FDA allowed Biogen to rely on the results of a clinical study of another company's interferon beta product, known as BG9015, after concluding that BG9015 was "comparable" to Avonex.

BG9015 was manufactured in Laupheim, Germany, by a joint venture owned half by Biogen and half by Rentschler Technology. **[\*\*4]** This joint venture commissioned Dr. Lawrence Jacobs to do a clinical study of BG9015 in the United States beginning in 1990. In 1993, while the clinical trial was going on, the joint venture failed and went into receivership. Production of BG9015 ceased, but researchers had enough BG9015 to complete the clinical trials, which ended in 1994. AR 2, 157-58.

As early as 1991, Biogen had begun separately producing interferon beta products similar to BG9015 at a manufacturing site in Cambridge, Massachusetts. After the Biogen-Rentschler joint venture failed, Biogen sought FDA approval of a new interferon beta, known as BG9216. Rather than conduct new clinical trials of BG9216, Biogen sought to rely on the Jacobs study and sought to demonstrate to FDA that BG9216 and BG9015 were comparable. The FDA concluded that BG9216 and BG9015 were not comparable, however, and declined to consider data from the Jacobs study in connection with the application of BG9216. AR 2.

Biogen then developed the interferon beta cell line that ultimately became Avonex and submitted it for FDA approval. Although FDA had invariably required full-scale clinical trials for new biological drugs in the past, Biogen again [\*\*5] sought to rely on the results of the Jacobs study conducted on BG9015, asserting that Avonex was comparable to BG9015. This time FDA agreed. After extensive biological, biochemical, and biophysical analyses, as well as pharmacokinetic studies in humans, FDA concluded that BG9015 and Avonex were "comparable" -- that they were "biochemically and functionally equivalent" -- and permitted the Jacobs study to be used in place of a separate clinical trial of Avonex itself. AR 2-10, 55-57.

Before Avonex could be approved for sale in the face of Betaseron's exclusivity under the Orphan Drug Act, FDA also had to make a finding that Avonex was "different" from Betaseron. FDA made that finding, basing its conclusion on the substantially less frequent occurrence of the death of skin tissue in the injection area, or injection site necrosis, associated with Avonex. n2 AR 29. FDA also noted that four percent of Avonex patients experience injection site reactions, such as swelling, redness or tenderness, compared to 85 percent of Betaseron patients. On the basis of those comparisons, FDA found Avonex "clinically superior" to Betaseron and therefore "different" for Orphan Drug Act purposes.

n2 Injection site necrosis sometimes requires surgical drainage or skin grafting for proper treatment. Concerns about injection site necrosis from Betaseron prompted a clinical report published in the New England Journal of Medicine. AR 502.

[\*\*6]

On May 17, 1996, FDA approved Avonex "for the treatment of relapsing forms of multiple sclerosis to slow the accumulation of physical disability and decrease the frequency of clinical exacerbations." AR 1.

Approximately three weeks before FDA approved Avonex, it issued and published in the Federal Register a "guidance document." This document stated that FDA regulations permit the approval of biological products on the basis of "clinical data generated from a [\*23] precursor product, made prior to a manufacturing change" so long as the manufacturer "can demonstrate that the precursor product is comparable to the manufactured product." FDA Guidance Concerning Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-derived Products ("Comparability Guidance Document"), 3. FDA did not cite or refer to the "comparability guidance

document" as a basis for its approval of Avonex. The principles and language embodied in the guidance document, however, were present in the document that announced FDA's approval of Avonex.

## ANALYSIS

As a preliminary matter, it should be noted that this decision proceeds from an examination not only of the pleadings, [\*\*7] but also of the administrative record. Defendants' motions have been treated as motions for summary judgment. *Marshall County Health Care Auth. v. Shalala*, 300 U.S. App. D.C. 263, 988 F.2d 1221, 1226 n.5 (D.C. Cir. 1993). Affidavits submitted by Berlex have not been considered, nor are they deemed to be part of the record of this case. See *Camp v. Pitts*, 411 U.S. 138, 142-43, 36 L. Ed. 2d 106, 93 S. Ct. 1241 (1973).

### 1. Elimination of Berlex's market exclusivity

Congress passed the Orphan Drug Act in 1983 to encourage the development of drugs for the treatment of rare diseases. n3 21 U.S.C. § § 360aa-360dd. The Act provides seven-year market exclusivity for orphan drugs and precludes the grant of FDA approval to other manufacturers of the same drug intended for treatment of the same disease. 21 U.S.C. § 360cc. [HN1] The statute does permit FDA approval of a drug that treats the same condition as did the original orphan drug if FDA determines that the two drugs are not the same. FDA's implementing regulations provide that a new drug will not be considered the same as a previously approved drug if the new drug is "clinically superior." 21 C.F.R. § 316.3(b)(13)(ii). [\*\*8] The regulations provide further that a new drug is "clinically superior" if it offers "greater safety in a substantial portion of the target populations . . ." 21 C.F.R. § 316.3(b)(3)(ii). Applying those regulations to Avonex and relying primarily upon the disparity in the incidence of injection site necrosis caused by Betaseron (5%) and Avonex (0%), FDA concluded that Avonex was safer than Betaseron and therefore a "different" drug. AR 29, 502-03.

n3 [HN2] "Orphan drugs" are drugs that treat diseases 1) affecting fewer than 200,000 persons or 2) affecting more than 200,000 person for which there is no reasonable expectation that the cost of developing and marketing the drug will be recovered from sales in the United States. 21 U.S.C. § 360bb(2).

Berlex challenges FDA's decision that Avonex is "clinically superior" to Betaseron. Berlex argues that it was arbitrary and capricious for FDA to rely exclusively on a single side effect when making that determination

and contends that FDA should instead have compared [\*\*9] the "overall safety profiles" of Avonex and Betaseron.

The Orphan Drug Act is silent as to the nature of the analysis FDA must undertake when deciding whether one drug is clinically superior to another. [HN3] The regulations provide as an example of "greater safety" the elimination of "an ingredient or contaminant that is associated with relatively frequent adverse effects." 21 C.F.R. § 316.3(b)(3)(ii). FDA has interpreted its regulations to mean that even "a small demonstrated . . . diminution in adverse reactions may be sufficient to allow a finding of clinical superiority." 57 Fed. Reg. 62076, 62078 (Dec. 29, 1992). [HN4] That interpretation is entitled to the court's deference. *Lyng v. Payne*, 476 U.S. 926, 939, 90 L. Ed. 2d 921, 106 S. Ct. 2333 (1986).

FDA's application of that interpretation in a specific case must be upheld if the agency based its decision upon relevant factors that have evidentiary support. *Ritter Transportation, Inc. v. ICC*, 221 U.S. App. D.C. 312, 684 F.2d 86, 88 (D.C. Cir. 1982), cert. denied, 460 U.S. 1022, 75 L. Ed. 2d 494, 103 S. Ct. 1272 (1983). The substantial disparity between Avonex and Betaseron with regard to injection site necrosis was surely [\*\*10] a factor relevant to safety, and Berlex does not challenge the sufficiency of [\*\*24] the record evidence on that point. FDA had an adequate basis upon which to consider Avonex "clinically superior" to Betaseron, and its decision that Avonex is "different" for purposes of the Orphan Drug Act will not be disturbed.

## 2. Approval of Avonex without separate clinical trials

Berlex next asserts that FDA's approval of Avonex without requiring Biogen to conduct its own clinical trials contravened the Public Health Service Act ("PHSA") and FDA regulations issued thereunder. Biogen and FDA acknowledge FDA's past insistence upon clinical trials of each drug being considered for approval, but they contend that no statute or regulation requires it and submit that the use of data on "comparable" drugs is within FDA's discretion. In addition, Biogen argues that Berlex lacks standing to complain under the PHSA of the approval of a competitor's drug. The standing question, of course, must be addressed first.

### a. Standing

[HN5] Prudential standing to challenge an agency decision exists if the challenger is within the "zone of interest to be protected or regulated by the statute . . ." Association [\*\*11] of Data Processing Serv. Orgs. v. Camp, 397 U.S. 150, 153, 25 L. Ed. 2d 184, 90 S. Ct. 827 (1970). A plaintiff has no right to bring suit against an

agency, however, "if the plaintiff's interests are so marginally related to or inconsistent with the purposes implicit in the statute that it cannot reasonably be assumed that Congress intended to permit the suit." *Clarke v. Securities Indus. Ass'n*, 479 U.S. 388, 399, 93 L. Ed. 2d 757, 107 S. Ct. 750 (1987). There is no evidence suggesting that Congress created the PHSA to protect Berlex's economic interest in particular, or competition among drug manufacturers in general. Berlex's standing thus depends on whether its interests "coincide with the protected interests" of the PHSA in such a way that Berlex is a "suitable challenger" of FDA's decision. *Hazardous Waste Treatment Council v. Thomas*, 280 U.S. App. D.C. 296, 885 F.2d 918, 922-23 (D.C. Cir. 1989).

The present action is obviously driven by Berlex's economic interest in maintaining Betaseron's market position. That motivation, however, does not deprive Berlex of standing. As the Court of Appeals recently concluded, [HN6] "a plaintiff who has a competitive interest in confining [\*\*12] a regulated industry within certain congressionally imposed limitations may sue to prevent the alleged loosening of those restrictions, even if the plaintiff's interest is not precisely the one that Congress sought to protect." *First Nat'l Bank & Trust v. Nat'l Credit Union*, 300 U.S. App. D.C. 314, 988 F.2d 1272, 1277 (D.C. Cir. 1993).

The question that must be resolved is whether the objectives of the PHSA are more likely to be frustrated or promoted by Berlex's claim. *Scheduled Airlines Traffic Offices, Inc. v. Department of Defense*, 87 F.3d 1356, 1359 (D.C. Cir. 1996) (citations omitted); *First Nat'l Bank & Trust*, 988 F.2d at 1275 (quoting *Clarke*, 479 U.S. at 397 n.12). Here, Berlex alleges that FDA has failed to comply with a statute that is focused on the safety and efficacy of new drugs.

On facts remarkably similar to those of the present case, the Third Circuit recently confirmed a drug manufacturer's standing to challenge FDA approval of a competing drug. *Schering Corp. v. FDA*, 866 F. Supp. 821 (D.N.J. 1994), aff'd, 51 F.3d 390 (3d Cir.), cert. denied, 133 L. Ed. 2d 195, 116 S. Ct. 274 (1995). The district court in that case held that [HN7] the manufacturer [\*\*13] of a "pioneer" drug had standing to sue the FDA for its alleged failure to enforce safety and efficacy standards against a competitor. The court reasoned that the interests of the plaintiff and the FDA were "systematically aligned" in such a way as to promote the principal safety objective of the statute and that the manufacturer was thus a "suitable challenger" for standing purposes. *Id.* at 825. The Third Circuit affirmed, observing that the pioneer drug manufacturer was "well-positioned to monitor the FDA regulations implementing statutorily mandated requirements . . .

when it is their pioneer drug the generic manufacturer seeks to copy." *Schering Corp. v. FDA*, 51 F.3d 390, 396 (3rd Cir. 1995). The court, in particular, emphasized [\*25] that the economic interest of the plaintiff provided an incentive for the plaintiff to advocate the "overriding necessity of ensuring public access to safe commercial drugs." *Id.*

Berlex's interests are aligned sufficiently with those of the intended beneficiaries of the PHSA. As a manufacturer of a similar product that was recently approved, Berlex has both the expertise and the incentive to monitor FDA's actions. Berlex's challenge, whatever [\*\*14] its merits, has required the FDA to justify its acknowledged departure from past drug approval procedures and to explain its conclusions that reliance on clinical tests of a "comparable" product will not compromise the statutory requirement of "safety, purity, and potency." 42 U.S.C. § 262(d)(1). Berlex has standing to bring this claim under the PHSA.

#### b. FDA approval process

[HN8] The PHSA authorizes FDA to license biological products that "meet standards designed to insure the continued safety, purity, and potency of such products . . ." 42 U.S.C. § 262(d)(1). FDA's regulations require applicants for licenses to "submit data derived from nonclinical laboratory and clinical studies which demonstrate that the manufactured product meets prescribed standards of safety, purity, and potency . . ." 21 C.F.R. § 601.2(a). No quantitative or measurable "standards" for safety, purity or potency exist. The regulations do, however, set out definitions of those terms that guide FDA's case-by-case determinations. 21 C.F.R. § 600.3. n4

n4 For example, the regulations define "safety" as "the relative freedom from harmful effect to persons affected, directly or indirectly, by a product when prudently administered, taking into consideration the character of the product in relation to the condition of the recipient at the time." 21 C.F.R. § 600.3(p).

[\*\*15]

Neither the PHSA itself nor FDA's regulations issued under the PHSA provide that the clinical study offered to demonstrate the safety, purity and potency of a new biological product shall have been conducted on that very product. The absence of a specific provision on this point raises the now-standard question of whether the agency's view of what is "appropriate in the context of this particular program is a reasonable one." *Chevron, U.S.A., Inc. v. Natural Resources Defense Council, Inc.*,

467 U.S. 837, 845, 81 L. Ed. 2d 694, 104 S. Ct. 2778 (1984). [HN9] FDA's policies and its interpretation of its own regulations will be paid special deference because of the breadth of Congress' delegation of authority to FDA and because of FDA's scientific expertise. *Lyng v. Payne*, 476 U.S. 926, 939, 90 L. Ed. 2d 921, 106 S. Ct. 2333 (1986); see *Bristol-Myers Squibb Co. v. Shalala*, 923 F. Supp. 212, 216 (D.D.C. 1996).

FDA's decision in this case to allow Biogen to rely on the clinical trials of BG9015 was based upon a reasonable interpretation of the PHSA and FDA regulations. FDA conceded that it had never before approved a new biological drug on the basis of a clinical study of a "comparable" [\*\*16] drug, but FDA demonstrated by reference to public documents that the principle of comparability was not unknown and that, in fact, it had been previously applied in other situations. FDA argues that its extension of the comparability principle in this case reflects a reasonable interpretation of the statutory grant of its regulatory authority, particularly given the rapidly changing scientific and technological context in which FDA regulates biological products. The record contains ample support for FDA's comparability determination and for its finding that Avonex is "safe, pure and potent" as required by the statute. This court may not substitute its own judgment for that of the FDA, an agency created by Congress to address difficult scientific issues such as the one at the center of this claim.

### 3. Comparability Guidance Document

Berlex's third claim focuses on FDA's issuance, on April 25, 1996, of the "guidance document" that explained FDA's position on comparability. Berlex had predicted (accurately) that the guidance document would prove to be the harbinger of FDA's decision on May 17, 1996, to approve [\*26] Biogen's license applications for Avonex. n5 Berlex's argument [\*\*17] now is that the guidance document was unlawfully issued without the notice-and-comment rulemaking required by the APA.

n5 The original complaint in this action, filed on April 26, 1996, sought to enjoin FDA from approving Avonex. Plaintiff's application for a temporary restraining order was denied on April 30, 1996.

The guidance document, which lays out FDA's policy for accepting clinical trials completed on "comparable" products, was published three weeks before FDA approved Avonex. The relationship between FDA's issuance of the guidance document and its approval of Avonex is not clear. FDA and Biogen both

point out that the guidance document was not mentioned in the administrative record. FDA's explanation -- that "the agency applied the policy described in the comparability guidance" but "did not rely on the guidance in doing so" -- is murky. FDA's Opposition to Plaintiff's Motion for Summary Judgment, 7. For purposes of this analysis it will be assumed that (1) FDA attached considerable importance to the [\*\*18] comparability guidance document and (2) the issuance of the guidance document and the approval of Avonex were in fact related events. Those assumptions make it necessary to address Biogen's claim that the guidance document was improperly issued.

[HN10] The APA requires notice-and-comment rulemaking when an agency issues new "legislative" or "substantive" rules that establish binding norms having the force of law. 5 U.S.C. § 553; *American Mining Congress v. Mine Safety & Health Admin.*, 302 U.S. App. D.C. 38, 995 F.2d 1106, 1109 (D.C. Cir. 1993). "Interpretive" rules, however, are expressly excused from the notice-and-comment requirements. 5 U.S.C. § 553(b)(3)(A). An interpretive rule is one "issued by an agency to advise the public of the agency's construction of the statutes and rules which it administers." *Shalala v. Guernsey Memorial Hosp.*, 131 L. Ed. 2d 106, 115 S. Ct. 1232, 1239 (1995). In this circuit, a rule is legislative, rather than interpretive, if any one of the following four questions is answered in the affirmative:

- (1) whether in the absence of the rule there would not be an adequate legislative basis for . . . agency action to confer benefits or ensure the [\*\*19] performance of duties,
- (2) whether the agency has published the rule in the Code of Federal Regulations,
- (3) whether the agency has explicitly invoked its general legislative authority, or
- (4) whether the rule effectively amends a prior legislative rule.

*American Mining Congress*, 995 F.2d at 1112.

In this case, all four questions are answered in the negative. First, as noted in the previous section of this memorandum, FDA had statutory authority to approve Avonex without requiring clinical trials. Second, the rule was not published in the Code of Federal Regulations. Third, the agency did not invoke its general legislative authority with respect to the guidance document. And fourth, the comparability guidance document did not effectively amend a legislative rule because it neither repudiates nor is inconsistent with any pre-existing FDA regulations. See *Shalala v. Guernsey Memorial Hosp.*,

131 L. Ed. 2d 106, 115 S. Ct. 1232, 1239 (1995); *National Family Planning and Reproduction Health Ass'n, Inc. v. Sullivan*, 298 U.S. App. D.C. 288, 979 F.2d 227, 235 (D.C. Cir. 1992).

The existing FDA regulation requires the submission of "data derived from nonclinical laboratory [\*\*20] and clinical studies." 21 C.F.R. § 601.2(a). In the guidance document, FDA interpreted that language to include data from clinical studies completed on "comparable" biological products. Comparability Guidance Document, 3. That interpretation extended the boundaries of previous FDA actions and policies, to be sure, but it did not "run[] 180 degrees counter to the plain meaning of the regulation," as did the agency directive at issue in *National Family Planning and Reproduction Health Ass'n, Inc. v. Sullivan*, 298 U.S. App. D.C. 288, 979 F.2d 227, 235 (D.C. Cir. 1992). In *National Family Planning*, the Department of Health and Human Services had announced to the public that its interpretation of a regulation (concerning the provision of abortion counseling by physicians) was [\*\*27] clear and definitive, and that interpretation was indeed upheld by the Supreme Court. Under different political leadership, the agency then issued a "directive," without notice-and-comment rulemaking procedures, that effectively reversed its earlier position. The Court of Appeals set the agency action aside, ruling that the agency had amended a legislative rule. 979 F.2d at 231-32. In this case, by contrast, [\*\*21] FDA's decision to rely upon the clinical trial of a "comparable" drug was not a reversal of course. It was a policy development with identifiable antecedents.

Nor has Berlex succeeded in demonstrating that the guidance document conflicts with any other FDA regulation. Berlex's assertion of potential conflicts that might arise between the comparability guidance document and other FDA regulations at some future time falls short of a showing that clear inconsistencies now exist.

Because the comparability guidance document was interpretive and not legislative, its issuance did not require notice-and-comment rulemaking.

## CONCLUSION

FDA did not act unlawfully when it: 1) determined that Avonex is "clinically superior" to Betaseron; 2) approved Avonex for use by patients with MS without requiring clinical trials of Avonex; and 3) issued its comparability guidance document without notice-and-comment rulemaking. FDA's determination that Avonex is safe, pure and potent is amply supported by the record. An appropriate order accompanies this memorandum.

James Robertson

United States District Judge

October 7, 1996

**ORDER**

For the reasons stated in the accompanying memorandum, [\*\*22] it is this 7th day of October, 1996,

**ORDERED** that plaintiff's motion for summary judgment [# 48] is **DENIED**. It is

**FURTHER ORDERED** that defendants' motions to dismiss [# 36, # 39] are treated as motions for summary judgment and **GRANTED** and this case is **DISMISSED**.

James Robertson

United States District Judge