

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

BERLEX LABORATORIES, INC.,

Plaintiff,

v.

FOOD AND DRUG ADMINISTRATION,
et al.

Defendants,

BIOGEN, INC.,

Intervenor-
Defendant.

Civil Action 96-0971 (JR)

MEMORANDUM IN SUPPORT
OF DEFENDANTS' MOTION TO DISMISS

INTRODUCTION

In this action, plaintiff Berlex challenges the scientific basis upon which the Food and Drug Administration (FDA) has issued a license for Avonex™, a product manufactured by the intervenor in this action, Biogen. Berlex alleges that FDA's decision is arbitrary and capricious under the Administrative Procedure Act (APA).

However, FDA's decision is reasonable in all respects and is supported by the administrative record. The principal argument advanced by Berlex, that FDA inappropriately used data from a "different" product to approve Avonex, is without merit. The allegedly "different" product is not different in any relevant respect, as demonstrated by extensive scientific data comparing Avonex with its precursor product. In fact, the allegedly "different" product was actually developed by Biogen in

conjunction with another company, Rentschler, that is associated with plaintiff Berlex. Also, FDA rejected an earlier license application by Biogen because Biogen did not demonstrate that that product was comparable to the precursor product.

This case is similar to six recent cases in which pharmaceutical manufacturers have attempted to block competition by challenging the scientific basis upon which FDA approved their competitors' products. All of those challenges have failed. See The Upjohn Company v. Kessler, No. 4:96-CV-90 (W.D. Mich. April 30, 1996) (attachment A hereto); Bristol-Myers Squibb Co. v. Shalala, 923 F. Supp. 212 (D.D.C. 1996); Schering Corp. v. FDA, 51 F.3d 390 (3d Cir.), cert. denied, 116 S.Ct. 274 (1995); Glaxo, Inc. v. Shalala, No. 94-1323 (JHG) (D.D.C. July 22, 1994) (this was attachment B to defendants' opposition to Berlex's motion for a temporary restraining order); Fisons Corp. v. Shalala, 860 F. Supp. 859 (D.D.C. 1994); Schering Corp. v. Sullivan, 782 F. Supp. 645 (D.D.C. 1992), vacated as moot sub nom., Schering Corp. v. Shalala, 995 F.2d 1103 (D.C. Cir. 1993).

The instant case is simply another example of a manufacturer inappropriately seeking to bar competition in the marketplace. For these reasons and the reasons outlined below, plaintiff's complaint should be dismissed.

STATEMENT OF THE CASE

Along with its original complaint filed on April 26, 1996, Berlex moved this Court for a temporary restraining order (TRO) and preliminary injunction to prevent FDA from approving Avonex.

On April 30th, this Court denied plaintiff's request for a TRO, and stayed judicial action until FDA made a formal decision on Biogen's product license application (PLA) and establishment license application (ELA) for Avonex.

On May 17, 1996, FDA approved Biogen's application for a marketing license for Avonex and served on the parties and the Court publicly releasable portions of the administrative record supporting its decision (in this brief this redacted portion of the record is cited as "AR"). The entire administrative record has been identified and made available to plaintiff's attorneys; however, it cannot be made available to others absent Biogen's agreement or a protective order, and plaintiff's motion for a protective order is pending before this Court. On June 7, 1996, plaintiff filed an amended complaint seeking declarative and injunctive relief pursuant to the APA ("Am. Complaint"). Plaintiff alleges that FDA's decisions to approve Avonex under the Public Health Service Act and to grant it market exclusivity under the Orphan Drug Act are arbitrary and capricious. Plaintiff also alleges that a document issued by FDA to provide guidance regarding comparability between biological products is a rule that should have been published for comment under the APA.^{1/}

^{1/} This document, "FDA Guidance Concerning Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-Derived Products," was Exhibit 10 to Plaintiff's Memorandum in Support of its Motion for Temporary Restraining Order. In this brief, the Guidance Document will be referred to as the "Comparability Guidance" or "Guidance Doc.", and plaintiff's TRO memorandum is referred to as "Pl. TRO Mem.". A copy of the guidance document is attached hereto at Tab B for the Court's convenience.

FDA now moves this Court to dismiss because plaintiff cannot show that FDA's approval of Avonex was arbitrary, capricious, and not in accordance with law, nor can it show that the guidance document should have been published for notice and comment.^{2'}

STATUTORY AND REGULATORY BACKGROUND

I. THE PUBLIC HEALTH SERVICE ACT

The Public Health Service Act (PHSA), 42 U.S.C. § 262, and the Federal Food, Drug, and Cosmetic Act (FDCA), 21 U.S.C. § 301-399, govern the regulation of biological products^{3'} in the United States. The PHSA requires that, prior to marketing, a manufacturer obtain FDA approval of its biological product license application. 42 U.S.C. § 262(a). The PHSA provides that FDA may issue such licenses "upon a showing that the establishment and the products for which a license is desired meet standards, designed to insure the continued safety, purity, and potency of such products." 42 U.S.C. § 262(d)(1).

FDA has implemented a regulatory scheme for issuing biological licenses. See 21 C.F.R. Part 600. The application for approval is commonly called a product license application, or PLA. In addition, a manufacturer may have to obtain an establishment license application, or ELA, by demonstrating that

^{2'} Inasmuch as this motion does not go beyond the administrative record, a motion to dismiss under Federal Rule of Civil Procedure 12(b)(6) is proper. Marshall County Health Care Auth. v. Shalala, 988 F.2d 1221, 1225-27 (D.C. Cir. 1993).

^{3'} Biological products are defined as any "virus, therapeutic serum, toxin, antitoxin, vaccine, blood ... , or analogous product." 42 U.S.C. § 262(a).

the establishment used to manufacture the licensed product meets standards designed to assure the product's continued safety, purity, and potency.^{4/} Potency is defined as the specific ability of the product to effect a given result.

21 C.F.R. § 600.3(s).

This regulatory scheme governs biological drug products made from new, innovative technologies, which are known as biotechnology-derived or biotech products. In recent years, scientific and technological developments have made it possible for manufacturers to "create" biological products using certain advanced technical and scientific methods. These include recombinant deoxyribonucleic acid (DNA)-derived proteins, or rDNA products.^{5/}

^{4/} Biological products intended for human use are drugs within the meaning of the FDCA because they are "intended for use in the ... cure, mitigation, [or] treatment ... of disease in man." 21 U.S.C. § 321(g)(1)(B). As a result, certain requirements applicable to drugs also apply to biologic drug products. These include the requirement that sponsors conduct clinical studies under an investigational new drug application (IND), 21 C.F.R. § 312.2(a), and that they be manufactured in accordance with current good manufacturing practice (CGMP) requirements. 21 C.F.R. Parts 210 and 211.

^{5/} As explained in defendants' opposition to plaintiff's motion for a TRO, both Avonex and plaintiff's biological product, Betaseron, are rDNA products. rDNA products are made by inserting a human gene into a cell so that the cell, known as the "host" cell, then produces and secretes a certain protein. The host cell used in this case is a Chinese hamster ovary (CHO) cell. The host cell and the human gene are selected to produce a desired protein. The host cell secretes the desired protein into a medium. The manufacturer purifies the protein from the medium using a chromatography process which is designed to result in a very pure protein bulk drug substance. See Alberts, Bruce, et al., Molecular Biology of the Cell, pp. 167-74, 258-71 (2nd ed. 1989); AR 156-57.

The advent of new technologies has raised questions about how FDA should regulate products produced using rapidly-changing technological processes. FDA has responded by issuing informal guidance to the industry interpreting the manner in which existing regulatory requirements apply to the development and production of biotech products. This guidance has allowed technology to develop and has permitted FDA to adapt its regulations to new scientific, technological, and commercial developments. FDA's regulatory approach has given the biotechnology industry some flexibility while protecting the public through FDA review of product safety, purity, and potency.

In order to understand the context in which this guidance has been issued, it is necessary to understand that, traditionally, a biological product was often defined by its manufacturing process. Comparability Guidance at 1. FDA has recognized that changes in the manufacturing process, equipment, or facilities used to make a biologic could result in changes to the biologic itself. Id. at 1-2. Therefore, if a manufacturer wanted to change the process used to manufacture a product after clinical data had been submitted to FDA in an application, FDA sometimes required additional clinical studies to demonstrate that the finished product was as safe, pure, and potent as the "precursor" (or pre-change), product. Id. at 2. However, not all changes require such clinical studies if the precursor product is comparable to the post-change product. FDA has

provided guidance in recent years to assist the industry in determining when such studies should be done.

For example, in 1990, FDA's Center for Biological Evaluation and Research (CBER) published a guidance document governing cytokine products, which include interferons. See "Cytokine and Growth Factor Pre-Pivotal Trial Information Package" (Cytokine Guidance Doc.).^{9/} This document addressed, among other things, the question of whether manufacturers must perform clinical studies before implementing changes in the manufacturing process used to make Cytokine products. In this document, CBER noted that "[s]ignificant changes in the manufacturing process ... may result in the need to conduct additional ... in vitro studies (non-clinical) and/or clinical studies." Id. at 4-5 (emphasis added). FDA did not say that such studies were required.

In 1994, CBER published "Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use" (mAb Guidance Doc.) See 59 Fed. Reg. 39571 (August 3, 1994) (notice of availability). In it, CBER stated that FDA would not always require clinical studies: "Depending on the type of in vitro assays and animal studies and quality of the data, extensive clinical data demonstrating equivalence may not be necessary.... When changes in manufacture occur late ... in clinical development, additional clinical evaluation may be requested if biochemical and functional characterization of mAb

^{9/} These guidance documents are public and plaintiff has copies of them. If the Court would like copies of these documents, the defendants will provide them.

indicate that the older and newer products differ." mAB Guidance Doc. at 21 (emphasis added).

Similarly, in April of 1995, FDA acknowledged that manufacturers make changes in cell lines, or master cell banks, used to manufacture rDNA products. 60 Fed. Reg. 17535, 17537 (April 6, 1995) (Changes to be Reported for Product and Establishment License Applications, Guidance). FDA requires that such changes be reported to the agency, id. at 17536-37, 21 C.F.R. § 601.12(a), but does not prohibit such changes or automatically require that new clinical studies be conducted before such changes may be made.

The most recent of these guidance documents -- the one challenged by plaintiff -- further addresses the issue of product comparability. Recent improvements in production methods and tests used to "characterize" a biologic allow manufacturers to identify and assess the impact of changes made to production processes and production facilities. Comparability Guidance at 3. Manufacturers can now perform analytical testing, bioassays, pharmacokinetic studies, and preclinical animal studies to compare precursor products with the final, finished biological product they seek to license. Id. at 5-6. On the basis of its review of comparability data, FDA may not require manufacturers to perform additional clinical studies after a manufacturing change is implemented. Id. at 8.

Thus, FDA may approve a manufactured product based, in part, upon data from clinical studies performed upon its precursor

product. This data, combined with other information, can be used by FDA to determine whether a product is comparable to its precursor product.

II. THE FOOD, DRUG, AND COSMETIC ACT

Biological products are also subject to the FDCA, see note 4 supra, including its provisions intended to promote the development of products for the treatment of rare diseases or disorders. These provisions are commonly known as the Orphan Drug Act, and specifically apply to biologics. 21 U.S.C. §§ 360aa-dd.

The Orphan Drug Act was enacted by Congress to provide incentives for the development of drug products that are intended for such a small patient population that the sponsors' potential financial gain from them is small. See generally Genentech, Inc. v. Bowen, 676 F. Supp. 301 (D.D.C. 1987). To encourage the development of such drugs, Congress instructed FDA to assist companies in designing research on the drugs, provided grants and tax incentives to companies which enter the field, and granted approved orphan drug products market exclusivity for seven years. See 676 F. Supp. at 303; 21 U.S.C. § 360cc(a).

To be considered an orphan drug within the meaning of the FDCA, a biological product's sponsor submits a request to FDA for designation as an orphan product. 21 U.S.C. § 360bb(a)(1)(C). If FDA determines that the disease or condition for which the product is intended affects fewer than 200,000 people at the time of the sponsor's request for orphan designation, the product is

designated as an orphan biologic. 21 U.S.C. § 360bb(a)(2). Such a designation permits FDA to assist the sponsor in designing research, and allows the sponsor to claim certain tax incentives. See 26 U.S.C. § 28. More than one applicant can receive orphan designation for products intended to treat the same disease or condition. 21 U.S.C. § 360bb(a)(1). Once a biological drug that has obtained orphan designation is approved for the designated indication, the agency is precluded from approving an application for the same drug intended for the same use for seven years. 21 U.S.C. § 360cc(a).

FDA has promulgated rules governing orphan products' market exclusivity. 21 C.F.R. Part 316. The rules allow the sponsor of a second product to demonstrate to FDA that its product is different from the first product. 21 C.F.R. § 316.3(b)(12). The second product is considered a different drug if it either has a different molecular structure or is clinically superior to the first product. Id. § 316.3(b)(13).

There are several ways that the sponsor of a second product may show clinical superiority; one of them is by demonstrating that the product is safer than the first product, another is by demonstrating greater effectiveness. Id. § 316.3(b)(3). Upon such a showing, FDA may approve the second product and grant it market exclusivity. FDA promulgated this rule to implement the Congressional desire to provide incentives for the development of the best possible products for patients with rare diseases or

disorders. See 56 Fed. Reg. 3338 (Jan. 29, 1991) (Proposed Rule: Orphan Drug Regulations).

FACTUAL BACKGROUND

I. BIOGEN'S APPLICATION FOR MARKETING

In 1990, FDA received an application for an investigational new drug application (IND) from Dr. Lawrence D. Jacobs in Buffalo, New York. AR 365. Dr. Jacobs proposed to perform clinical tests on an interferon-beta product to determine whether it was safe and effective for the treatment of multiple sclerosis. AR 365-66. FDA allowed the IND to go into effect and Dr. Jacobs performed his study using interferon beta manufactured by a company called Bioferon. AR 2, 11-12, 150. Bioferon was a company owned jointly by plaintiff's affiliate, Rentschler Biotechnologie, and Biogen. AR 2. Some of the labels for this product indicate that it was manufactured by Bioferon for Biogen. AR 380-83.

Biogen, not Bioferon, communicated with FDA regarding issues concerning the Jacobs study. AR 362-63, 367, 370, 374, 376. In 1990, Biogen submitted to FDA information concerning the manufacturing process used to make the product in a drug master file. AR 367-69. As a result, Biogen is the "holder" of the manufacturing data included in the master file and may reference that data to support a product application. 21 C.F.R. § 314.420.

Shortly thereafter, Bioferon dissolved. Pl. TRO Mem., Exh. 1(C) at 6. Biogen either had or obtained the rights to the clinical study data gathered by Dr. Jacobs, and Rentschler

retained the master cell bank used to manufacture the product upon which Dr. Jacobs' study was performed. Id.

Biogen then embarked upon research and development of interferon beta. AR 2, 157. After doing so, it submitted a PLA and ELA for Avonex to FDA in 1995.^{2/} The PLA includes the data gathered by Dr. Jacobs in his clinical trial. AR 2, 157. In order to use the Jacobs data, Biogen had to demonstrate to FDA that its product, Avonex, is comparable to the product used in the Jacobs study. AR 55.^{3/}

Comparability may be shown through analytical testing; biological assays; pharmacokinetic, pharmacodynamic, and toxicity studies; and human clinical studies. See Comparability Guidance at 5-7. Biogen submitted the results from biochemical tests assessing whether the molecules in the two products are structurally similar; these tests analyzed the molecules' structure in a variety of ways. AR 3; 55-57. Biogen also conducted a series of *in vitro* bioactivity tests (tests conducted outside a living organism) to evaluate whether the two interferon molecules have the same ability to stimulate a particular response in cells. AR 3, 57. FDA also reviewed the results of

^{2/} Biogen had submitted to FDA data concerning an interferon product it had developed in 1992, but the agency determined that this product was not comparable to the product used in the Jacobs study (this 1992 product is identified as BG9216). AR 2.

^{3/} The product used in the Jacobs study is also known as BG9015. Herein and in the Administrative Record it is referred to as BG9015, 9015, the Bioferon product, the Avonex precursor product, or the Jacobs study product. Avonex is also referred to as BG9418.

in vivo studies (conducted within a living organism) performed on animals and humans that evaluated Avonex's toxicity and pharmacokinetic profile. AR 7-8.

Based upon these comparability data, FDA made a determination that the clinical data supporting the safety and effectiveness of the Bioferon product could also be used to support the safety and effectiveness of Avonex. AR 2. On December 4, 1995, FDA's Peripheral and Central Nervous System Drugs Advisory Committee met and voted that the Jacobs study data was adequate to demonstrate the safety, purity, and potency of Avonex. Pl. TRO Mem. Exh. 5 (transcript of Advisory Committee meeting) at 125-28. After evaluating the data provided by Biogen, FDA approved Avonex for marketing in the United States on May 17, 1996. See Defendant's Notice of Filing of Administrative Record, attachment 1.

II. BIOGEN'S ORPHAN DRUG ACT APPLICATION

While FDA was reviewing these nonclinical and clinical data, FDA's Office of Orphan Product Development considered whether Avonex could be allowed on the market under the orphan drug provisions of the FDCA. Biogen submitted a request for orphan designation to FDA in 1991. AR 521-42. FDA determined that the number of people with multiple sclerosis at the time of the request was less than 200,000, and designated Biogen's interferon beta product to be an orphan biologic. AR 543-46; 21 C.F.R. § 316.24(a). However, Berlex had also applied for and received orphan designation for its product, Betaseron™. FDA

approved Betaseron™ on July 23, 1993, for treatment of relapsing forms of multiple sclerosis. Am. Complaint ¶ 32. Therefore, Betaseron had market exclusivity within the meaning of the Orphan Drug Act. FDA could only approve Avonex if it determined that Avonex was different from Betaseron. 21 C.F.R. §§ 316.3(b)(13); 316.25(a)(3). After reviewing the data contained in the Avonex PLA, FDA determined that Avonex is clinically superior to Betaseron, and therefore different from it. See Defendant's Notice of Filing, attachment 2; AR 500; 502-05; 21 C.F.R. § 316.3(b)(13)(ii)(A).

Avonex is clinically superior to Betaseron for two reasons. The first has to do with an adverse reaction called injection site necrosis (death of tissue surrounding the injection site). None of the patients treated with Avonex have experienced injection site necrosis, while approximately five percent of those treated with Betaseron have such a reaction. AR 500-05. The second involves injection site reactions. Eighty-five percent of patients taking Betaseron experience some lesser type of injection site reaction, e.g. swelling, tenderness, or redness, while far fewer taking Avonex have such reactions (only four percent of the patients in the Jacobs trial experienced injection site reactions). AR 29, 503.

Based upon its analysis of the injection site necrosis and reactions caused by Betaseron and the absence thereof in Avonex patients, FDA determined that Avonex is clinically superior to Betaseron. AR 29, 500; Defendant's Notice of Filing, attachment

2. Therefore, Avonex is a different drug than Betaseron and FDA can approve it and grant it market exclusivity for seven years. Now that FDA has done so, MS patients will have the choice of taking either Avonex or Betaseron.

ARGUMENT

I. THERE IS A REASONABLE BASIS FOR FDA'S DECISION TO APPROVE AVONEX AND TO GRANT IT MARKET EXCLUSIVITY

A. The Standard of Review

In an Administrative Procedure Act (APA) case such as this, the standard of review is highly deferential to the agency:

[T]he court must consider whether the decision was based on a consideration of the relevant factors and whether there has been a clear error of judgment.... Although this inquiry into the facts is to be searching and careful, the 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, Inc. v. Volpe, 401 U.S. 402, 416 (1971) (citations omitted). "[T]here is a presumption in favor of the validity of administrative action." Ethicon, Inc. v. FDA, 762 F. Supp. 382, 386 (D.D.C. 1991).

Deference is especially due when the challenged action involves the application of the agency's scientific expertise. See, e.g., Baltimore Gas & Electric Co. v. Natural Resources Defense Council, Inc., 462 U.S. 87, 103 (1983); International Fabricare Inst. v. EPA, 972 F.2d 384, 389 (D.C. Cir. 1992) ("The rationale for deference is particularly strong when [the agency] is evaluating scientific data within its technical expertise"). Courts have been especially deferential to FDA for this reason. See, e.g., Henley v. FDA, 77 F.3d 616, 621 (2d Cir. 1996) ("FDA

possesses the requisite know-how to conduct such [scientific] analyses, by sifting through the scientific evidence to determine the most accurate and up-to-date information regarding a particular drug We therefore defer to its reasonable findings."); Tri-Bio Laboratories, Inc. v. United States, 836 F.2d 135, 142 (3d Cir. 1987) ("in evaluating scientific evidence in the drug field, the FDA possesses an expertise entitled to respectful consideration by this court"), cert. denied, 488 U.S. 818 (1988).

Where, as here, Congress has not spoken directly to the issue, and "Congress has explicitly left a gap for the agency to fill, there is an express delegation of authority to the agency to elucidate a specific provision of the statute by regulation." Chevron, U.S.A. Inc. v. Natural Resources Defense Council, Inc., 467 U.S. 837, 843-44 (1984). Inasmuch as this action involves in part an interpretation by FDA of its own statute and regulations, deference is especially important. Id. at 844-45; United States v. Rutherford, 442 U.S. 544, 553 (1979).

In applying the arbitrary and capricious standard, the court reviews the administrative record assembled by the agency and does not undertake its own fact finding. See, e.g., Camp v. Pitts, 411 U.S. 138, 142 (1973); Upjohn v. Schweicker, 681 F.2d 480, 483 (6th Cir. 1982). As long as the agency provides the "determinative reason for the final action taken," Camp v. Pitts, 411 U.S. at 143, and there is any reasonable basis for that decision, it will be upheld.

Applying these standards, it is apparent that FDA's approval of Avonex should be upheld.^{9/}

- B. There Exists a Reasonable Scientific Basis for FDA to Conclude that Avonex is Safe, Pure, and Potent Pursuant to the Public Health Service Act.

As outlined above, the PHSA provides that FDA may issue a biological product license upon a showing that the establishment and the product meet standards designed to insure the product's "safety, purity, and potency." 42 U.S.C. § 262(d)(1). Biogen submitted and FDA reviewed thousands of pages of scientific data concerning Avonex prior to making this determination. See, e.g., Defendant's Notice of Filing; AR. Biogen submitted an ELA which contained detailed information about the facilities in which Avonex is manufactured, and FDA inspected these facilities. AR 289-91. FDA corresponded at length with the company concerning the adequacy of the nonclinical and clinical study data contained in the PLA, and requested supplemental information on various issues. See AR 225-236.

Plaintiff simply cannot show that this scientific information is inadequate to support approval of Avonex. In

^{9/} Berlex's alleged threat to its reputation, stemming from consumer confusion resulting from "misleading press reports" is too vague and speculative to satisfy the Article III injury-in-fact requirement for any of its allegations. Am. Complaint ¶ 54. The chain of events that must follow for Berlex to be harmed in this manner is highly attenuated and relies entirely on the hypothetical actions of third parties, not FDA. Such injury is too speculative for Article III purposes. "The injury requirement will not be satisfied simply because a chain of events can be hypothesized in which the action challenged eventually leads to actual injury." Northwest Airlines, Inc. v. FAA, 795 F.2d 195, 201 (D.C. Cir. 1986). Therefore, plaintiff cannot assert this injury.

fact, plaintiff does not even seriously argue that this information is, in itself, inadequate. Instead, plaintiff argues that FDA's decision on Avonex is improper because FDA improperly relied on clinical data from the Bioferon-manufactured product. Am. Complaint ¶ 64.^{10/} However, there is extensive support in the record to support FDA's conclusion that the two products are comparable, and thus FDA's reliance on the clinical data from the Bioferon product (BG9015) is reasonable.

1. Comparison of Avonex and BG9015

Proteins are chains of amino acids that are linked together by chemical bonds. There are a total of 20 different amino acids, and a protein may contain some or all of the 20 amino acids. Each protein is unique because of the arrangement, or sequence, of the particular amino acids used to construct the protein. The interferon beta-1a protein is a chain of these amino acids in 166 positions in a specific sequence. See AR 1-2. The sequence of amino acids allows the protein to fold into a specific three-dimensional structure that enables the protein to act as a drug. It is important that the protein be created in such a way that it has the correct three-dimensional structure.

There are several ways of determining whether two different proteins are comparable in a medical sense. One method is to

^{10/} plaintiff does not argue that the clinical study on the Bioferon product is inadequate; in fact, plaintiff has stated that its affiliate, Rentschler, has sought to rely on the Jacobs study for its own purposes. See Transcript of hearing on Motion to Compel at 30-33 (May 31, 1996). Plaintiff simply does not want Biogen to use the study.

compare the structure of each protein. Another is to compare the manner in which the proteins act on cells, or the bioactivity of the proteins. Another is to compare how the proteins behave in human subjects. All of these analyses were done on the Bioferon-manufactured product (BG9015) and Avonex (BG9418).

a. Structure

Many tests were conducted that compared the structure of the Biogen product (BG9418) with the structure of the Bioferon (Rentschler) product (BG9015). Biogen conducted a biochemical test called a peptide map which showed that the Avonex and the Bioferon product have the identical amino acid sequence. See AR 3 (Peptide Map discussion); 55-57, 157.^{11/} A further analysis of these products, the Edman degradation, confirmed that the two products were in fact composed of the same amino acids. AR 3. These results were also confirmed by N-terminal amino acid sequencing, which examines the specific amino acids, and their sequence, in the N-terminal, or one end, of the protein. AR 3. The results were also the same for the other end of the chain, the C terminal. Id. Although some of both 9015 and 9418 were missing the first amino acid, methionine, and the percentages of the molecules that were missing methionine were different, this difference was not significant because it did not affect the behavior of the proteins in biological tests. Id. Other procedures also revealed the similarity between 9015 and 9418: CD

^{11/} A peptide map is done on each lot of the product by the manufacturer, Biogen, in the normal course of events.

spectra for the two revealed that the shape of molecules was the same; and mass spectrometry revealed that disulfide bonding occurred at the same point in the amino acid chain for each protein. Id. Further, using a BIAcore analysis, a particular antibody that recognizes interferon in a particular way responded identically to both 9015 and 9418. Id.

Biogen also performed carbohydrate analysis on the two proteins using two methods, electrophoresis and mass spectrometry. These analyses detected that three major carbohydrates, or glycoforms, were identical and present in the same proportions for both proteins. AR 3 (carbohydrate analysis). Although there were some differences in minor glycoforms, they did not result in any detectable differences in the way in which the two proteins behaved in humans. Id. Immunoblotting, which was used to compare the size and the electrical charge of the molecules, also revealed no significant differences between the two proteins. AR at 3 (Immunoblotting analyses). Although there were some differences in this regard, they did not affect the manner in which the proteins behaved. Id.

Another test, reverse phase high pressure liquid chromatography (HPLC) also revealed no difference between the two proteins. There was some deamidated product in both proteins (this is when one amino acid in the chain is changed into another amino acid). AR 3 (reverse phase HPLC). This change, which is common in proteins, occurred in both products and did not result

in any differences in bioactivity between the Bioferon product and Avonex. Id.

This material comparing the structure of the two proteins provides overwhelming evidence that the two are comparable. The other two types of analysis provided confirmation of this fact.

b. Bioactivity

FDA also evaluated the results of tests that Biogen performed to determine whether the two products' molecules have the same bioactivity. Biological studies, or bioassays, measure the ability of interferon beta to stimulate a particular response in cells that is dependent upon binding to a molecule on the cell surface called a receptor. The two products bind to its receptor on cells in a virtually identical manner. Both products exhibited essentially identical anti-viral bioactivity, or prevented the killing of the same number of viral-infected cells. Id. at 3-4. Also, both exhibited the same anti-growth bioactivity in certain cells; that is, they inhibited growth in an identical manner. Id. Further, both products increased a specific type of antigen (MHC Class I) to the same extent. Id.

c. Pharmacokinetic Comparison

FDA evaluated tests of Avonex which Biogen performed in animals and human subjects. The human study compared the absorption, distribution, and elimination by the human body -- the pharmacokinetic profile -- of BG9015 and BG9418. This human pharmacokinetic study revealed that both products are present in the blood stream at similar levels at regular time intervals

following their injection. This study was a cross over study,^{12/} and was performed on healthy volunteers to avoid interference from the patient's underlying disease state or from other drugs the patient might have been taking. The study revealed that the products' pharmacokinetic profiles are not different. See AR 7-8 (Pharmacokinetic Comparability Study).^{13/}

The animal studies were evaluated to determine the biochemical, pharmacologic, and safety activity of 9015 and 9418. The animal studies revealed that none of these products depart from the type of behavior that FDA has observed in other, approved interferon products. See AR 9-10 (Preclinical Pharmacology and Toxicology).

These results, when taken together, demonstrated to FDA that Avonex is comparable to the Bioferon-produced interferon beta

^{12/} A cross over study is one in which each subject is given both products (at different times) and thus the behavior of each drug is observed in the same subjects. A cross over study is considered the best type of study for analyzing comparability, and the results of Biogen's study are extremely persuasive.

^{13/} plaintiff attacks FDA's bioequivalence finding by asserting that Biogen's clinical study is flawed because it was conducted in healthy volunteers rather than patients with multiple sclerosis. Am. Complaint ¶ 49. However, FDA does not require that bioequivalence testing be performed in sick patients. Bioequivalence testing is done to assess the manner and rate by which the body absorbs the drug product. Absorption may be affected by the disease the patient has or other drugs the patient may be taking while participating in clinical trials. Therefore, it is sometimes preferable for bioequivalence studies to be performed on healthy volunteers. Cf. 21 C.F.R. § 320.24 (FDA's bioequivalence regulation pertaining to new drug applications (not biologics): "The selection of the method used to meet an in vivo or in vitro testing requirement depends upon the purpose of the study, the analytical methods available, and the nature of the drug product.").

product which Jacobs tested in his clinical trial. Based upon these assessments, FDA relied on the Jacobs study, among other things, and concluded that Avonex is safe, pure, potent, and effective.

2. FDA Regulations Allow FDA to Evaluate Nonclinical Comparability Study Data and Clinical Study Data To Approve a Biological Product

Perhaps realizing that the scientific basis for FDA's decision is unassailable, plaintiff is left to argue, in essence, that the Avonex approval is "different" from past FDA biological product approvals. See Am. Complaint ¶¶ 14-15. Plaintiff does not provide examples of products that have been presented to FDA that were situated similarly to Avonex and not approved. Plaintiff essentially argues that because a situation exactly like that of Avonex has not occurred previously, FDA cannot approve Avonex. In other words, FDA cannot apply its regulations, policies, and practices to a situation that is not precisely like one it has seen before. The regulatory rigidity plaintiff advocates is not the law. If it were, agencies could not function, and a rapidly-changing field like the biotechnology industry would be stifled.

FDA's approval of Avonex did not involve a change in agency regulation, policy, or practice, but the application of existing policies and practices to a situation that was similar to, but not exactly the same as, prior situations. In fact, FDA regulations allow FDA to adapt to new situations; i.e., to do

what it did here -- accept comparability assessments in approving biological licenses.

The Public Health Service Act gives FDA broad authority to design standards for biological products. 42 U.S.C. § 262(d)(1). FDA has promulgated a regulation that requires a product's manufacturer, or sponsor, to submit to FDA "data derived from nonclinical laboratory and clinical studies which demonstrate that the manufactured product meets prescribed standards of safety, purity, and potency" in order to receive a license. 21 C.F.R. § 601.2(a). This regulation leaves to FDA decisions about the amount, type, and scope of clinical and nonclinical data necessary to demonstrate that a product is safe, pure, and potent.

FDA makes these determinations on a case-by-case basis, and, when doing so, allows manufacturers to demonstrate through nonclinical studies that a finished product is comparable to a precursor product upon which clinical studies were performed. See Comparability Guidance at 8. This interpretation of the regulations is entirely reasonable and is within FDA's discretion. See Udall v. Tallman, 380 U.S. 1, 16-17 (1965).

Where, as here, Congress has not spoken directly to the issue and the agency has elucidated its interpretation of the statute in regulations, the question before the court is whether the agency's view of what is "appropriate in the context of this particular program is a reasonable one." Chevron, 467 U.S. at 845. Plaintiff points to absolutely nothing to show that FDA's

interpretation of the regulations to allow comparability assessments is unreasonable.

In fact, FDA has issued a series of related guidances in the past several years indicating that it would rely on comparability assessments when approving products. As discussed supra, in 1990 CBER published a guidance document governing cytokine products, which include interferons. In that document CBER noted that, while "changes in the manufacturing process ... may result in the need to conduct additional ... studies and/or clinical studies," such additional studies are not required each time a manufacturing change occurs.

Similarly, in the mAb Guidance Document, CBER specifically stated that FDA would not always require clinical studies for manufacturing or production changes. mAb Guidance Doc. at 20-21. Thus, for several years the public has been aware that comparability may be shown through means other than clinical studies. Also, as noted above, in April of 1995, FDA acknowledged that manufacturers make changes in cell lines, or master cell banks, used to manufacture rDNA products. 60 Fed. Reg. at 17537.

The comparability guidance document that plaintiff challenges is also clear in this regard. The document "describes current FDA practice concerning product comparability of human biological products." Comparability Guidance at 1. "FDA has examined proposed manufacturing changes on a case-by-case basis to determine the type of data, including clinical data, that were

necessary to determine product comparability." Id. at 2. As a result, it "has approved manufacturing changes made during or after completion of clinical studies in situations where comparability data have provided assurance that the product is safe, pure, and potent." Id. The document "interprets the phrase 'data derived from nonclinical laboratory and clinical studies' ... in 21 C.F.R. § 601.2(a)." Id. at 3. Therefore, the guidance document does not change agency policy or practice, but interprets terms which appear in FDA regulations.^{14/}

In fact, FDA has applied these interpretations to several products in recent years. Pursuant to supplements to applications received from manufacturers, FDA has permitted manufacturers to make changes in manufacturing processes without additional studies. See Summary Basis of Approval and FDA Scientific Reviews for Epoetin-alfa approval (change in facilities used for manufacturing product); FDA approval of amendment for Satumomab Pendetide Product License (change in equipment used in manufacturing and in purification process); FDA approval of Amendment for Epoetin-alfa Product License (change in

^{14/} Even if the comparability policy were a change in agency practice, nothing in the law prohibits FDA from informally changing its past interpretation. Chevron, U.S.A., 467 U.S. at 863-64; Natural Resources Def. Counsel v. EPA, 822 F.2d 104, 112 (D.C.Cir. 1987); Center for Science v. Dept. of Treasury, 797 F.2d 995, 999 (D.C. Cir. 1986). The question is whether the agency gives a reason for any change in position. Id. As outlined above, FDA carefully explained, through various guidance documents, its policies and practices on the comparability issue.

product formulation); FDA Approval of amendment for Alteplase product license (change in cell formulation and purification).^{15/}

Although the changes made with respect to these products are not exactly the same as the changes regarding Avonex, these FDA decisions reflect a systematic approach of establishing comparability between old and new products. These examples demonstrate that a mechanism is in place to deal with these situations and that FDA did not "change" its behavior with respect to Avonex.

For these reasons, plaintiff's complaint fails to state a claim and should be dismissed.

C. There Exists a Reasonable Scientific Basis for FDA to Conclude that Avonex is Safer than Betaseron and, Therefore, Eligible for Market Exclusivity

Plaintiff asserts that FDA was arbitrary and capricious when it determined that Avonex is safer than Betaseron. Am. Complaint ¶ 66. As the comparability issue, this issue involves FDA's scientific judgment, is within the agency's scientific and technical expertise, and was resolved reasonably.

The record demonstrates that Avonex is safer than Betaseron. AR 29; 500; 502-03. FDA analyzed the adverse reactions caused by Betaseron and compared them to adverse reactions caused by Avonex. AR 502. During its clinical trial, Betaseron caused a serious adverse reaction -- injection site necrosis (death of the

^{15/} These examples were cited in defendants' opposition to plaintiff's motion for a TRO, at 8. Copies of these documents have been made available to plaintiff, and can be made available to the Court.

tissue surrounding the injection site) -- in five percent of patients. Id. After marketing, Berlex reported to FDA that approximately 216 patients had been treated for skin necrosis at the injection site. Id., 309-10. Some of them have had surgery to remove dead tissue around the injection site and some have had skin grafting to treat the affected area. Id.

MS patients treated with Avonex have not suffered from this adverse reaction. AR 502. Furthermore, patients in a currently on-going clinical safety trial of Avonex have been taking the drug for six months or longer -- the period of time during which most patients taking Betaseron develop necrosis. AR 229, 503. In addition, many more patients suffer from injection site reactions with Betaseron than with Avonex. Id. Therefore, there is adequate scientific evidence to show that Avonex is safer than, and therefore different from, Betaseron. 21 C.F.R. §§ 316.3(b)(3)(ii) and 316.3(b)(13)(ii).

Plaintiff attacks FDA's analysis of the safety profile of the two products by alleging that FDA "only" compared one potential adverse event caused by Betaseron. Am. Complaint ¶ 52. Plaintiff attempts to cast aspersions upon Avonex for "other adverse events, such as herpes reactivation" which Betaseron does not cause. Id. A reading of the Summary of the Administrative Record belies plaintiff's accusations, however. The clinical review of Avonex, AR 149-248, contains a detailed analyses of Avonex's safety. AR 206-214. The review notes that the herpes reactivation plaintiff cites occurred in four percent of study

patients taking Avonex and three percent of patients taking the placebo. AR 208. Therefore, the risk that Avonex causes herpes reactivation does not reach statistical significance. AR 211.

There is no requirement in the regulations that FDA find a significant reduction in numerous adverse events in order to declare a product safer than another -- reduction of one adverse reaction is sufficient. 21 C.F.R. § 316.3(b)(3)(ii); 57 Fed. Reg. 62076, 62078 (Dec. 29, 1992) ("a small demonstrated improvement in efficacy or diminution in adverse reactions may be sufficient to allow a finding of clinical superiority"). Furthermore, head-to-head clinical trials comparing Avonex and Betaseron are not required. See 21 C.F.R. § 316.3(b)(3)(ii). As a result, existing data is sufficient to allow FDA to approve Avonex and allow the drug to compete with Betaseron. This approval gives patients a treatment alternative.

Plaintiff has simply failed to come forward with any evidence to show that FDA's decision to approve Avonex was arbitrary, capricious, and not in accordance with law.

D. The Public Interest

As defendants argued in their opposition to plaintiff's request for a TRO, Congress enacted the Orphan Drug Amendments "to facilitate the development of drugs for rare diseases or conditions." H.R. Rep. No. 97-840, Part 1, 97th Cong. 2d Sess. at 5 (1982), reprinted in 1982 U.S.C.C.A.N. at 3577. The statutory language and the legislative history together demonstrate a clear intent by Congress to reward companies that

invest the time and money necessary to develop drugs for patients with rare diseases. FDA's implementing regulations also allow for the development and marketing of clinically superior orphan drug products. 21 C.F.R. §§ 316.3(b)(3) and 316.3(b)(13). As FDA stated, "orphan drug exclusive approval does not preclude significant improvements in treating rare diseases." 56 Fed. Reg. 3338 (January 29, 1991). In short, the public benefits when better drugs become available through FDA approval.

Were the Court to reverse FDA's approval of Avonex, it would be limiting patients' access to a safer drug product for people suffering from relapsing multiple sclerosis. This is simply not in the public's interest. Furthermore, in 1991 FDA published its intention to allow the development of a safer product which could break Betaseron's exclusivity. See 56 Fed. Reg. 3338. Therefore, Berlex has been on notice since before Betaseron was approved that a safer product could break its exclusivity. In this instance, Berlex merely wants to use this Court to limit its competition from a safer product.

Allowing this type of lawsuit to go forward does nothing but encourage companies to use the courts to stifle competition and second-guess a highly scientific regulatory decision. As discussed above, many courts have recognized that FDA is the most appropriate forum to address the complex scientific issues surrounding drug product approval. "The parties' dispute is fundamentally a scientific one over which the court lacks expertise and over which the FDA is expert. The court therefore

cannot conclude ... that the agency's decision was arbitrary and capricious." Bristol-Myers Squibb Co. v. Shalala, 923 F. Supp. at 220. See also Schering Corp. v. FDA, 51 F.3d at 399 ("The FDA is the agency charged with implementing the Food, Drug and Cosmetic Act as amended. Its 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."); The Upjohn Co. v. Kessler, Slip Op. at 16 (attachment A hereto) ("Upjohn's dispute with the [FDA] memorandum is fundamentally a scientific dispute in an area where this Court lacks expertise and is required to give the FDA great deference."); Glaxo, Inc. v Shalala, Slip Op. at 16 (Attachment B to the government's TRO memorandum) ("it is not for the Court to decide which of the competing scientific procedures is preferable.").

The public does not benefit from increased litigation or from the inevitable uncertainty that litigation brings to a product's approval and marketing. For these reasons, this Court should reject Berlex's efforts to overturn FDA's approval of Avonex.

II. THERE HAS BEEN NO VIOLATION OF
THE APA NOTICE AND COMMENT PROVISIONS

Plaintiff also argues that FDA has violated the APA by enacting a rule without notice and comment. Am. Complaint ¶¶ 55-62. The "rule" allegedly enacted is one that permits FDA to approve "biological products without clinical testing." Am. Complaint ¶ 57.

However, as the discussion above makes clear, FDA has no such "rule." In any event, the guidance document challenged by Berlex is not a "rule" that required publication for notice and comment under the APA, and plaintiff's allegation is meritless.

The APA defines "rule" as "the whole or a part of an agency statement of general or particular applicability and future effect designed to implement, interpret, or prescribe law or policy or describing the organization, procedure, or practice requirements of an agency:..." 5 U.S.C. § 551(4). "Legislative" (or "substantive") rules, interpretative rules, and statements of policy are all treated as rules under the APA definition. Legislative rules establish binding norms that have the force of law, American Mining Congress v. Mine Safety and Health Admin., 995 F.2d 1106, 1109 (D.C. Cir. 1993), and must be promulgated in accordance with the notice and comment procedures of the APA. 5 U.S.C. § 553. These notice and comment requirements do not apply to "interpretative rules, general statements of policy, or rules of agency organization, procedure or practice." 5 U.S.C. § 553(b).

A recent case from in this Circuit demonstrates that the guidance document at issue here is not a substantive rule. In American Mining Congress, the court announced the following test to determine whether a rule has "legal effect" and is therefore "legislative." If any of these four criteria are met, it is an indication that the rule is legislative:

(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.

Id. at 1112.

Under this test, the comparability guidance document is clearly not a legislative rule: In its absence, there would be an adequate statutory and regulatory basis for the Avonex approval; the document was not published in the CFR; FDA did not invoke its legislative authority; and the rule did not amend a prior legislative rule.

The guidance document is, at most, an interpretation or a non-binding statement of agency policy, and was not required to be published under the APA. Interpretative rules do not create law, grant or deny rights, or impose obligations which do not already exist by statute. American Mining Congress, 995 F.2d at 1109. Rather, interpretive rules remind affected parties of existing duties. National Latino Media Coalition v. FCC, 816 F.2d 785, 787-88 (D.C. Cir. 1987). They do not determine the rights of private parties or conclusively resolve issues addressed in the rule. National Latino Media Coalition, 816 F.2d at 788. See also United Technologies Corp. v. EPA, 821 F.2d 714, 718 (D.C. Cir. 1987); General Motors Corp. v. Ruckelshaus, 742 F.2d 1561, 1565 (D.C. Cir. 1984) (en banc), cert. denied, 471

U.S. 1074 (1985); Gibson Wine Co. v. Snyder, 194 F.2d 329, 331 (D.C. Cir. 1952).^{16/}

A statement of policy is issued by an agency to advise the public of the manner in which an agency proposes to exercise a discretionary power. American Mining Congress, 995 F.2d at 1109; Pacific Gas & Electric Co. v. Federal Power Comm'n, 506 F.2d 33, 38 (D.C. Cir. 1974). Such statements are non-binding in nature. Pacific Gas & Electric Co., 506 F.2d at 38. Also, publication of a policy "facilitates long range planning within the regulated industry and promotes uniformity in areas of national concern."

Id.

The comparability guidance document interprets an FDA regulation and explains an agency policy. The PHSA and its implementing regulations constitute the applicable law governing the regulation of biological drugs. The statute gives FDA broad discretion to "design" and "prescribe" standards for product licenses. 42 U.S.C. § 262(d). Similarly, the regulations allow

^{16/} The notice and comment procedures of the APA are not triggered simply because a rule has a substantial impact on a large number of people, American Postal Workers Union v. USPS, 707 F.2d 548, 560 (D.C. Cir. 1983), cert. denied, 465 U.S. 1100 (1984); Cabais v. Egger, 690 F.2d 234, 237-38 (D.C. Cir. 1982), or even if it effects a change in policy, American Postal Workers Union, 707 F.2d at 559-60; Orengo Caraballo v. Reich, 11 F.3d 186, 196 (D.C. Cir. 1993) (discussing American Postal Workers Union, the court state that an agency's change in its interpretation of a regulatory requirement is "not subject to the rulemaking requirements under [the APA] because both the old and new methods were interpretive rules."); Spartanburg General Hosp. v. Heckler, 607 F. Supp. 635, 643 (D.S.C. 1985) ("A mere change . . . is not automatically substantive . . .").

FDA to specify what type of nonclinical and clinical data it will evaluate in a particular application. 21 C.F.R. § 601.2(a).

The comparability guidance document explains the type of "data derived from nonclinical laboratory and clinical studies" that manufacturers may submit to FDA pursuant to 21 C.F.R. § 601.2(a). It does not require anything specific of manufacturers, nor does it require FDA to evaluate comparability testing results in a particular manner. In fact, the document "addresses the concept of product comparability and describes current FDA practice.... It describes those steps that manufacturers may perform and which FDA may evaluate to allow manufacturers to make manufacturing changes without performing additional clinical studies to demonstrate safety and efficacy Manufacturers may follow the procedures outlined in this document or may choose to use alternative procedures." Comparability Guidance at 1 (emphasis added). The document goes on to describe those tests that manufacturers "may use" to demonstrate the comparability of two products. Id. at 5-7. When, as here, the agency has described the type of tests that manufactures may perform and submit to FDA as part of a product license application, it has not created law, but simply interpreted an FDA regulation and described FDA policy for reviewing biological product licenses.

The guidance document is not "finally determinative" of whether a particular license is granted for a biological product. See American Bus Ass'n, 627 F.2d 525, 531 (D.C. Cir. 1980). Put

another way, the comparability document describes a manner of determining comparability; the agency must still determine whether a particular product is safe, pure, and potent pursuant to the statute and its implementing regulations. Significantly, the comparability document does not limit FDA's discretion. Nothing in the APA requires the agency to use rulemaking in these situations.

In fact, many courts have recognized that guidance documents similar to the one at issue here are not subject to notice and comment. In Brock v. Cathedral Bluffs Shale Oil Co., 796 F.2d 533 (D.C. Cir. 1986), the court held that "Enforcement Policy and Guidelines for Independent Contractors," which were used a "guidance in making individual enforcement decisions," were not required to be published. Id. at 535-38. In American Mining Congress v. Marshall, 671 F.2d 1251 (10th Cir. 1982), the court held that a "strategy" outlining how the Secretary planned to enforce a standard was not required to be published. Id. at 1262-63. The Fifth Circuit, in Professionals and Patients for Customized Care v. Shalala, 56 F.3d 592, 597 (5th Cir. 1995), and Southeastern Minerals, Inc. v. Harris, 622 F.2d 758, 766 (5th Cir. 1980), recognized that FDA Compliance Policy Guides (CPGs) do not require rulemaking procedures. See also Panhandle Producers v. ERA, 847 F.2d 1168, 1174-75 (5th Cir. 1988) (Economic Regulatory Administration guidelines relating to approval of natural gas imports were statements of policy, not binding rule; rulemaking not required); Mercury Motor Express.

Inc. v. United States, 648 F.2d 315, 319 (5th Cir. 1981) (ICC order announcing new criteria for approving for-hire operating authority applications was policy statement); Cowdin v. Young, 681 F. Supp. 366, 370 (W.D. La. 1987) (CPGs are not binding legal requirements).

For these reasons, plaintiff's argument that the guidance document should have been published for notice and comment must be rejected.

CONCLUSION

For the foregoing reasons, plaintiff's complaint should be dismissed.

Respectfully submitted,

FRANK W. HUNGER
Assistant Attorney General

ERIC H. HOLDER
United States Attorney

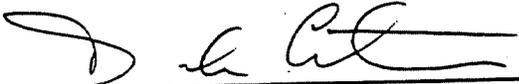
Of Counsel:

MARGARET JANE PORTER
Chief Counsel

MEREDITH MANNING
Assistant Chief Counsel

MARK RAZA
Associate Chief Counsel
U.S. Food and Drug
Administration
5600 Fishers Lane
Rockville, MD 20857

Dated: July 3, 1996


DRAKE CUTINI
Attorney
Office of Consumer Litigation
U.S. Department of Justice
P.O. Box 386
Washington, D.C. 20044
(202) 307-0044