

A TALE OF TWO PROTEINS:
THE FDA'S UNCERTAIN INTERPRETATION OF
THE ORPHAN DRUG ACT

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I. INTRODUCTION

One of the most difficult problems in science and technology policy is the creation of an appropriate legal framework for the development of new drugs.¹ The incentives for the development of new drugs are significantly affected by legal issues, from the scope of intellectual property protection to the expense and difficulty of obtaining marketing approval, which in the United States is granted by the Food and Drug Administration (“FDA”).² In our largely private, market-oriented system of health care, the rate of development of new drugs and other medical innovations is primarily determined by the financial incentives that are expected to be generated by successful development. Thus, the scope of intellectual property protection and the FDA approval process may well be the primary factors in determining the rate of production in the pharmaceutical and biotechnology industry.

The difficulty inherent in providing adequate incentives for new drug development is starkly revealed in the special legal framework created to stimulate the development of new drugs for small patient populations. Pharmaceutical companies generally spend many millions of dollars to develop a single new drug.³ This significant up-front

1. The difficulty of the problem may be seen in the long battle over FDA reform, which most recently produced section 1 of the Food and Drug Administration Modernization Act of 1997, Pub. L. 105-115, §1, 111 Stat. 2296 (1997).

2. *See id.*

3. *See* Joseph A. DiMasi, *The Cost of Innovation in the Pharmaceutical Industry*, 10 J. HEALTHCON. 107, 125–26 (1991) (estimating that before a new drug is introduced in the United States market, an average of 12 years and \$231 million is spent on drug

investment naturally leads companies to focus their development efforts on diseases where the patient populations are sufficiently large, so that the predicted product market share will generate an adequate return on investment. When the number of potential consumers who suffer from a rare disease is relatively small, the general market-based incentives for the development of new pharmaceuticals may well be insufficient to induce commercial investment in the necessary research and development ("R&D").⁴

This market problem was the impetus for the Orphan Drug Act of 1983⁵ ("the Act").⁶ As Representative Henry Waxman, a co-sponsor of the Orphan Drug Act, said, "The naming of drugs for rare diseases as 'orphan drugs' was not done frivolously. . . . They are very much like children who have no parents, and they require special effort."⁷ Congress amended the Food, Drug, and Cosmetics Act⁸ to promote the development of drugs for people with "rare diseases or conditions."⁹ Congress announced its findings that

[1] because so few individuals are affected by any one rare disease or condition, a pharmaceutical company which develops an orphan drug may reasonably expect the drug to generate relatively small sales in comparison to the cost of developing the drug and consequently to incur a financial loss;

research and development). The actual cost of bringing a new drug to market is the subject of some debate, with widely varying estimates. See George Anders, *Vital Statistic: Disputed Cost of Creating a Drug*, WALL ST. J., Nov. 9, 1993, at B1.

4. See Gina M. Cavalier, Note, *Pushing Parentless Pharmaceuticals: Toward an International Home for "Orphan Drugs" and a Cure for "Zebra" Diseases*, 27 LAW & POL'Y INT'L BUS. 447, 447 (1996); see also David B. Clissold, *Prescription for the Orphan Drug Act: The Impact of the FDA's 1992 Regulations and the Latest Congressional Proposals for Reform*, 50 FOOD & DRUG L.J. 125, 126 (1995).

5. Pub. L. No. 97-414, 96 Stat. 2049 (1983) (codified as amended in scattered sections of 21 U.S.C. and 42 U.S.C.).

6. For a history of the Orphan Drug Act, see Marlene E. Haffner, *Orphan Products—Ten Years Later and Then Some*, 49 FOOD & DRUG L.J. 593 (1994); Clissold, *supra* note 4, at 126–30.

7. Egon Weck, *Medicine's "Orphans": Drugs for Rare Diseases*, in FROM TEST TUBE TO PATIENT: NEW DRUG DEVELOPMENT IN THE UNITED STATES (PLI Patents, Copyrights, Trademarks & Literary Property Course Handbook Series No. G4-3819, 1988), available in 256 PLI/PAT. 121, 210 (1988).

8. 21 U.S.C. § 301 (1994).

9. See Orphan Drug Regulations, 56 Fed. Reg. 3338, 3338 (1991) (to be codified at 21 C.F.R. pt. 316) (proposed Jan. 24, 1991) (discussing legislative intent to provide economic incentives) [hereinafter Proposed Regulations].

[2] there is reason to believe that some promising orphan drugs will not be developed unless changes are made in the applicable Federal laws to reduce the costs of developing such drugs and to provide financial incentives to develop such drugs¹⁰

This Article examines the Orphan Drug Act and one of the most important incentives it provides for the development of new drugs for rare diseases, a seven-year period of market exclusivity for new orphan drugs. The FDA has had difficulty interpreting the market exclusivity provisions of the Orphan Drug Act since its enactment.¹¹ The continuing uncertainties about the scope of protection that the Act provides for innovative products threaten the basic purposes of the Act. The FDA's recent interpretation of the Act raises numerous questions: Should market protection from the Orphan Drug Act depend on the physical and functional properties of the drug, or should the protection depend on the design of the clinical trial? Should there be a nexus between biochemical similarity and clinical superiority, or should a competing drug be brought to the market if its application to the FDA is based on a differently designed clinical trial? Should the market protection afforded by the Orphan Drug Act be commensurate with the effort required to bring the drug to the market? Should the market protection afforded by the Orphan Drug Act be analogous to the scope of patent protection? Finally, should the FDA provide clear rules, analogous to the *FDA Guidance Concerning Demonstration of Comparability of Human Biological Products*,¹² to assist orphan drug sponsors in their efforts to determine the non-comparability of two orphan drugs?

10. Orphan Drug Act, § 1, 96 Stat. 2049.

11. See Orphan Drug "Sameness" Definition Update Will Recognize New Science, PINK SHEET, May 11, 1998, at 19.

FDA is planning to update its definitions of orphan drug "sameness" and "difference" to address new issues related to biotechnology and biologics, FDA Office of Orphan Products Development Director Marlene Haffner said at a May 5 workshop in Brussels on rare diseases and orphan drugs.

"Same versus different keeps challenging us," Haffner stated at the meeting

Id.

12. CENTER FOR BIOLOGICS EVALUATION AND RESEARCH (CBER) & CENTER FOR DRUG EVALUATION AND RESEARCH (CDER), FDA GUIDANCE CONCERNING DEMONSTRATION OF COMPARABILITY OF HUMAN BIOLOGICAL PRODUCTS, INCLUDING THERAPEUTIC BIOTECHNOLOGY-DERIVED PRODUCTS (1996), available at <<http://www.fda.gov/cber/guidelines.htm>> and <<http://www.fda.gov/cber/gdlns/comptest.txt>> [hereinafter GUIDANCE DOCUMENT].

Part II of this Article provides a brief overview of the Orphan Drug Act and its incentives for pharmaceutical research in general and the biotechnology industry in particular. Part III is an introduction to the general scientific context of the problem of determining when two drugs are the same or different. Part IV looks at the history of Orphan Drug Act controversies concerning the issue of whether two drugs are the same or different as well as the development of the FDA's regulatory framework for this issue. Part V examines the most recent major controversy under the Act, the approval of two variant forms of interferon β (and the rejection of a third form). Part VI examines the problem of distinguishing between similar drugs in the context of patent law, particularly the doctrine of equivalents and the reverse doctrine of equivalents, in an effort to shed a comparative light on the issues of Orphan Drug Act exclusivity. Part VII asks whether rules similar to the FDA's policies concerning generic drugs and the comparability of biological molecules from different manufacturing sources, used in determining when two drugs are the same for other FDA purposes, should be used to provide guidance under the Act. Part VIII concludes that guidelines for "non-comparability" testing, particularly focused on bioavailability and bioequivalence, could significantly reduce the uncertainties which have continually plagued the FDA's administration of the Orphan Drug Act and would bolster the Act's incentives for innovative medical treatments for rare diseases.

II. AN OVERVIEW OF THE ORPHAN DRUG ACT

A. The Orphan Drug Act's Purpose and Incentives

A drug can be an "orphan drug" if it is for a "rare disease or condition"¹³ that affects fewer than 200,000 patients in the United States or for which there is no reasonable expectation that the cost of developing the drug for a disease will be recovered from sales in the United States.¹⁴ Ten to twenty million Americans (about 9% of all

13. 21 U.S.C. § 360bb (1994 & Supp. III 1997).

14. *See* 21 U.S.C. § 360ee(b)(2) (1994).

The term "rare disease or condition" means (1) in the case of a drug; any disease or condition which (A) affects less than 200,000 persons in the United States, or (B) affects more than 200,000 in the United States and for which there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from sales in the United States of such drug

Americans) suffer from more than 5,000 rare diseases.¹⁵ Furthermore, as the Human Genome Project uncovers more genetic causes of human diseases, this number will increase.¹⁶

The "main purpose of the Orphan Drug Act is to stimulate innovation" and to foster the development of "therapeutically superior drugs" for these smaller patient populations.¹⁷ The Orphan Drug Act is expressly aimed at both of the key drug development constraints — the cost and duration of the FDA approval process as well as the issue of intellectual property protection. The Orphan Drug Act promotes innovation by reducing the development costs of orphan drugs before FDA approval and by increasing the financial returns from the orphan drugs after approval. The development costs required to obtain FDA approval are reduced through several Orphan Drug Act provisions. The FDA provides help to pharmaceutical companies regarding the FDA's drug approval process,¹⁸ while the Orphan Products Board further

Id.

15. See 136 CONG. REC. H11, 931 (daily ed. Oct. 23, 1990) (statement of Rep. Bliley); 134 CONG. REC. S3686 (daily ed. Mar. 31, 1988) (statement of Sen. Metzenbaum).

16. TASK FORCE ON GENETIC TESTING, PROPOSED RECOMMENDATIONS OF THE TASK FORCE ON GENETIC TESTING (1997), available at <<http://www.med.jhu.edu/tfgtelsi>>.

Principle IV-3: The development and maintenance of tests for rare genetic diseases must be encouraged. With few exceptions, the commercial sector is devoting more resources to the development of tests for a handful of common disorders than it is to the multitude of rare disorders. In contrast to the common disorders, most rare disorders are single-gene in inheritance and have high penetrance. Consequently, tests for the rare disorders often have higher predictive value, although sensitivity may be a problem when there is allelic diversity or locus heterogeneity. Because their causation is less complex than many common diseases, single-gene disorders may be more amenable to the development of effective therapies.

Id.

17. Proposed Regulations, *supra* note 9, at 3338; see also *Genentech, Inc. v. Bowen*, 676 F. Supp. 301, 305–06 (D.D.C. 1987), citing H.R. Rep. No. 97-840 at 6, reprinted in 1982 U.S.C.C.A.N. 3577, 3577; 128 CONG. REC. S15307 (daily ed. Dec. 16, 1982) (statement of Sen. Kennedy) (remarks inserted in record); 128 CONG. REC. H9678 (daily ed. Dec. 14, 1982) (statement of Rep. Weiss) (remarks inserted in record); *Id.* at H9674 (statement of Rep. Waxman); 128 CONG. REC. S13226–27 (daily ed. Oct. 1, 1982) (statement of Sen. Nunn); *Id.* at S13224 (statement of Sen. Kassebaum); *Id.* at S13222–23 (statement of Sen. Hatch); 128 CONG. REC. H7650 (daily ed. Sept. 28, 1982) (statement of Rep. Goodling).

18. The FDA helps drug developers design clinical trials that conform to FDA regulatory requirements and shows them how to deal with the FDA review system. Small companies with little regulatory experience can thereby save time and money

simplifies matters by coordinating the federal agencies involved in drug research and regulations.¹⁹ The IRS provides tax breaks for expenses related to orphan drug development.²⁰ Furthermore, the FDA may help fund the clinical testing necessary for approval of an orphan drug.²¹ After approval, the intellectual property protection provisions of the Orphan Drug Act increase the financial returns for orphan drug sponsors by providing a seven-year term of exclusive marketing rights for the drug in the orphan disease population, thereby allowing the orphan drug's sponsor "to recoup the cost of development by capturing all revenues from the sale of the drug for the rare disease."²²

For manufacturers, the market exclusivity provision may be "by far the most important incentive offered by the Orphan Drug Act."²³ The FDA bars other approvals for the "same" drug for the same disease or condition as a first-approved drug until the seven-year period of exclusivity expires.²⁴ The Orphan Drug Act market protection is narrow, because only the use of that particular drug for treating the designated

during drug development. *See* 21 U.S.C. § 360aa(a) (1994 & Supp. III 1997) (orphan drug manufacturer may request from the FDA written recommendations for clinical and non-clinical tests necessary for approval). To receive FDA drug approval, however, the drug manufacturer is still responsible, under 21 U.S.C. § 355, for showing that the drug is safe and effective. *See* 128 CONG. REC. H7650 (daily ed. Sept. 28, 1982) (statement of Rep. Ratchford) (remarks inserted in record).

19. *See* 42 U.S.C. § 236 (1994).

20. *See* 26 U.S.C. § 45C (Supp. III 1997). An orphan drug developer (sponsor) may claim 50% of clinical trial costs as a credit against taxes owed. *See id.* § 45C(a). "According to the National Organization for Rare Disorders, 'tax credits for clinical research have been a minor incentive to some drug companies, while the high cost of pre clinical toxicology studies continues to act as a barrier to development of true orphan drugs.'" 136 CONG. REC. H6194 (daily ed. July 31, 1990) (statement of Rep. Stark).

21. The Act funds a total of \$12 million worth of clinical research grants annually. Each grant may cover as much as \$200,000 of direct costs per year for up to three years. The grants are aimed not at large companies but at smaller, research-oriented organizations.

The Secretary may make grants to and enter into contracts with public and private entities and individuals to assist in (1) defraying the costs of qualified testing expenses incurred in connection with the development of drugs for rare diseases and conditions, (2) defraying the costs of developing medical devices for rare diseases or conditions, and (3) defraying the costs of developing medical foods for rare diseases or conditions.

21 U.S.C. § 360ee(a) (1994).

22. H.R. REP. No. 99-153, *reprinted in* 1985 U.S.C.C.A.N. 301, 303.

23. *Waxman Bill Limits Seven-Year Exclusively Granted Orphan Drugs*, BIOTECHNOLOGY NEWSWATCH, May 7, 1990, at 4 (quoting Pharmaceutical Manufacturers Association President Gerald Mossinghoff).

24. *See* 21 U.S.C. § 360cc (1994 & Supp. III 1997).

rare disease is protected.²⁵ However, if the drug is not approved for any other medical indication, then the Orphan Drug exclusivity is essentially as effective as patent protection. A second pharmaceutical manufacturer may seek FDA approval of a different drug for the same disease (or the same orphan drug for different orphan diseases or non-orphan diseases) but the sponsor of a subsequent drug for the same disease bears the burden of proof to demonstrate that its drug is different.²⁶

In placing the burden of distinguishing its drug on the second orphan drug sponsor, the Orphan Drug Act parallels patent law, an older and more comprehensive body of law for providing exclusive rights as an incentive for innovation. Patent law generally favors innovators over competitors who did not bear the commercial risk of innovation.²⁷ The simple premise for market exclusivity, whether under the Orphan Drug Act or through a patent, is that awarding a monopoly to an innovative product is generally economically justified — despite the monopoly output restrictions and the correspondingly higher prices — when the investment in innovation would be unlikely without market protection.²⁸ Indeed, when enacting the Orphan Drug Act, Congress determined that the pharmaceutical industry needed these special economic incentives to undertake R&D.²⁹

B. The Procedures of the Orphan Drug Act

Qualification for orphan drug benefits is a two-step process: designation and drug approval. Following drug approval, the pharmaceutical manufacturer obtains a product license to sell the drug with the Orphan Drug Act's seven-year market exclusivity.

25. See 21 U.S.C. § 360bb(a) (1994 & Supp. III 1997).

If the Secretary finds that a drug for which a request is submitted under this subsection is being or will be investigated for a rare disease or condition and [if] . . . the approval, certification, or license would be for use for such disease or condition, the Secretary shall designate the drug as a drug for such disease or condition.

Id.

26. See Proposed Regulations, *supra* note 9, at 3343.

27. See *Hilton Davis Chem. Co. v. Warner-Jenkinson Co.*, 62 F.3d 1512, 1534 (Fed. Cir. 1995) (Newman, J., concurring), *rev'd*, 520 U.S. 17 (1997).

28. See, e.g., Martin J. Adelman & Friedrich K. Juenger, *Patent-Antitrust: Patent Dynamics and Field-Of-Use Licensing*, 50 N.Y.U. L. REV. 273, 290 (1975).

29. See H.R. REP. No. 97-840, *reprinted in* 1982 U.S.C.C.A.N. 3577, 3578-79.

1. Designation

A pharmaceutical manufacturer seeks orphan status designation for a drug by (1) certifying that the product is for a rare condition, (2) providing a scientific rationale for using the drug for that rare condition, and (3) providing supporting epidemiologic data.³⁰ The designation process is “intended to reduce the wasted expense and lost time that occur when sponsors carry out investigations under protocols that are unsatisfactory to FDA.”³¹ The required scientific rationale for the orphan drug’s usefulness need only be a “plausible hypothesis backed by some experimental evidence.”³² The sponsor may seek orphan drug status at any phase of the R&D process before submitting an application for marketing approval.³³

The Orphan Drug Act does not limit the number of drugs that may be designated for a particular rare disease.³⁴ If a first orphan drug has obtained market approval, however, the FDA must not approve an application for designation by a second sponsor until seven years have passed.³⁵ The FDA can grant orphan drug designation status to new versions of an already marketed drug, but the second, similar drug will not be approved unless the FDA determines that the second applicant’s drug shows clinical superiority to the already marketed drug.³⁶

30. See 21 C.F.R. § 316.20 (1999).

31. See Proposed Regulations, *supra* note 9, at 3338.

32. The FDA’s Orphan Drug Development Program, 4 U.S. REG. REP. 1–6 (1987).

33. See 21 C.F.R. § 316.23 (1999).

(a) A sponsor may request orphan-drug designation at any time in the drug development process prior to the submission of a marketing application for the drug product for the orphan indication.

(b) A sponsor may request orphan-drug designation of an already approved drug product for an unapproved use without regard to whether the prior marketing approval was for an orphan-drug indication.

Id.

34. See 21 U.S.C. § 360bb (1997); *see also* 21 C.F.R. § 316.20(a) (1999).

35. See 21 C.F.R. § 316.25(a) (1999).

FDA will refuse to grant a request for orphan-drug designation if . . . [a] drug . . . is otherwise the same drug as one that already has orphan-drug exclusive approval for the same rare disease or condition and the sponsor has not submitted a medically plausible hypothesis for the possible clinical superiority of the subsequent drug.

Id.

36. See 21 C.F.R. § 316.20(a) (1999).

A sponsor may request orphan-drug designation of a previously unapproved drug, or of a new orphan indication for an already marketed drug. In addition, a sponsor of a drug that is otherwise

2. Approval

While any sponsor of an orphan drug may receive the development-phase benefits of the Orphan Drug Act, only the first manufacturer to receive full FDA drug approval receives the exclusive marketing rights for any one drug.³⁷ Although the FDA is liberal in awarding orphan drug designation,³⁸ the standard for approval is consistently high.

The FDA drug approval process consists of pre-clinical studies testing the safety and possible efficacy of the drug in animals followed by three phases of clinical investigation.³⁹ The pharmaceutical

the same drug as an already approved orphan drug may seek and obtain orphan-drug designation for the subsequent drug for the same rare disease or condition if it can present a plausible hypothesis that its drug may be clinically superior to the first drug. More than one sponsor may receive orphan-drug designation of the same drug for the same rare disease or condition

Id.; see also Proposed Regulations, *supra* note 9, at 3340 ("Approval of such a subsequent drug during the first drug's period of exclusive approval for treatment of the same rare disease or condition would require evidence of the clinical superiority of the subsequent drug, however. The content of this evidence will depend on the nature of the superiority claimed."); Paul V. Buday, *Hints on Preparing Successful Orphan Drug Designation Requests*, 51 FOOD & DRUG L.J. 75, 80 (1996).

37. See 21 C.F.R. § 316.31 (1999); see also Proposed Regulations, *supra* note 9, at 3341 ("FDA interprets the act to accord exclusive approval only to the first drug approved. This interpretation means that other applicants, who may have invested substantial money and effort in supporting their applications, are barred from marketing for the 7-year period of exclusivity even though they filed before or shortly after the applicant whose product was approved.").

38. See Proposed Regulations, *supra* note 9, at 3340.

39. See Li-Hsien Rin-Laures & Diane Janofsky, Note, *Recent Developments Concerning the Orphan Drug Act*, 4 HARV. J.L. & TECH. 269, 271-72 (1991) (describing the FDA drug approval process). Before the FDA approves a drug, the sponsor must first determine the pharmacological and toxicological characteristics of the drug by conducting pre-clinical tests on laboratory animals or *in vitro*. See 21 C.F.R. § 312.23(a)(8) (1999). The second stage is a clinical investigation. A "clinical investigation" is "any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects." *Id.* § 312.3. To conduct a clinical investigation, the sponsor must submit an investigational new drug ("IND") application, containing the pre-clinical results and a plan for the clinical investigation. See *id.* § 312.23. The plan becomes more detailed as the clinical investigation becomes progressively more complex. The sponsor also submits IND Safety Reports (to detail any "serious adverse experience" or "unexpected adverse experience"), *id.* § 312.32, and Annual Reports (that report the progress of the investigation), *id.* § 312.33. No changes in the structure of the clinical investigation can be without permission from the FDA. See *id.* § 312.30. No investigational new drugs can be marketed commercially without FDA approval of the IND plan. See *id.* § 312.7. Once an IND plan is in place, the investigational new drug "is exempt from the pre-marketing approval requirements that

manufacturer must submit extensive scientific and medical data, including chemical, pharmacological, and clinical studies.⁴⁰ The marketing approval applications for both drugs and biologics must show that the products are “safe and effective” for their intended use.⁴¹

Two major exceptions to the seven year orphan drug market exclusivity are: (1) where the market exclusivity holder cannot provide sufficient quantities of the drug to patients who need it,⁴² and (2) where the market exclusivity holder consents to subsequent approvals.⁴³ The FDA must, before making a finding of nonavailability, give the market exclusivity holder notice and the opportunity to comment.⁴⁴ Orphan drugs typically spend less time in development than non-orphan drugs.⁴⁵

are otherwise applicable and may be shipped lawfully for the purpose of conducting clinical investigations of that drug.” *Id.* § 312.1(a). Phase I clinical trials test the drug’s safety and investigate potential side effects. *See id.* § 312.21(a). Phase II trials test the drug’s effectiveness in target patients. *See id.* § 312.21(b). Phase III tests provide additional information about the effectiveness and safety needed to evaluate the drug’s risk/benefit relationship and to provide the basis for appropriate drug labeling. *See id.* § 312.21(c). Clinical trials usually last from six to nine years. After the drug has been demonstrated to be safe and effective for human use, the sponsor of the drug applies to the FDA for approval to market the drug. *See id.* § 314.1. The results of the clinical investigations are submitted in a New Drug Application (“NDA”). If the FDA approves the NDA, the drug may be marketed.

40. *See* 21 C.F.R. § 601.2(a) (1999).

41. *See id.* § 314.2 (“The purpose of this part is to establish an efficient and thorough drug review process in order to: (a) Facilitate the approval of drugs shown to be safe and effective”); 42 U.S.C. § 262 (1994 & Supp. III 1997) (“The Secretary shall approve a biologics license application . . . on the basis of a demonstration that . . . the biological product that is the subject of the application is safe, pure, and potent.”).

42. *See* 21 U.S.C. § 360cc(b)(1) (1994 & Supp. III 1997).

[T]he Secretary may, during the seven-year period . . . , approve another application . . . if . . . the Secretary finds, after providing the holder notice and opportunity for the submission of views, that in such period the holder of the approved application or of the license cannot assure the availability of sufficient quantities of the drug to meet the needs of persons with the disease or condition for which the drug was designated

Id.

43. *See* 21 U.S.C. § 360cc(b)(2) (1994 & Supp. III 1997).

[T]he Secretary may, during the seven-year period . . . , approve another application . . . for such drug for such disease or condition for a person who is not the holder of such approved application . . . if . . . such holder provides the Secretary in writing the consent of such holder for the approval of other applications or the issuance of other licenses before the expiration of such seven-year period.

Id.

44. *See* 21 U.S.C. § 360cc(b)(1) (1994 & Supp. III 1997).

45. *See* Genentech, Inc. v. Bowen, 676 F. Supp. 301, 303 (D.D.C. 1987). In 1993,

This may be because an orphan drug application usually involves fewer patients and fewer clinical trials (which is inevitable for diseases with fewer sufferers).⁴⁶ Also, orphan drugs are often the only available treatment for the rare disease or condition, which is why orphan drug protection is necessary and commercially viable.⁴⁷ Furthermore, an orphan drug sponsor can seek FDA approval to allow patients access to the drug even before marketing approval, either through a Treatment IND⁴⁸ or an Orphan Drug open protocol.⁴⁹

orphan drugs were approved in an average of 12.8 months compared to 33.1 months for non-orphan drugs. See Marlene E. Haffner, *Applications of the Orphan Drug Act to Special Patient Populations*, 28 DRUG INFO. J. 495, 500–01 (1994). Orphan drugs that were new molecular entities (“NMEs”) were approved in an average of 12.4 months, again much faster than the 25.6 months for non-orphan NMEs. See Cavalier, *supra* note 4, at 453. “The 1994 median review time for all new chemical drugs was 17.5 months; the subset of drugs reviewed in 1994 under the user fee program was reviewed in a median time of 13.5 months.” PRESIDENT BILL CLINTON & VICE PRESIDENT AL GORE, REPORT OF THE NATIONAL PERFORMANCE REVIEW: REINVENTING REGULATION OF DRUGS AND MEDICAL DEVICES n.1 (Apr. 1995), available at <<http://www.fda.gov/po/reinvent.html>>.

46. See H.R. REP. NO. 97-840(I) (1982), reprinted in 1982 U.S.C.A.N. 3577, 3583 (“FDA has longstanding policy of approving NDA’s [sic] on the basis of studies with relatively few patients when the disease in question is rare and the benefit-risk considerations are clearly favorable.”).

47. See Haffner, *supra* note 46; see also New Drug, Antibiotic, and Biological Drug Product Regulations, 57 Fed. Reg. 58,942 (1992) (to be codified at 21 C.F.R. pt. 314 and pt. 601).

48. See 21 C.F.R. §§ 312.80–.88 (1999).

49. See 21 U.S.C. § 360dd (1994).

If a drug is designated under section 360bb of this title as a drug for a rare disease or condition and if notice of a claimed exemption under section 355(i) of this title or regulations issued thereunder is filed for such drug, the Secretary shall encourage the sponsor of such drug to design protocols for clinical investigations of the drug which may be conducted under the exemption to permit the addition to the investigations of persons with the disease or condition who need the drug to treat the disease or condition and who cannot be satisfactorily treated by available alternative drugs.

Id. “FDA commits itself to encourage sponsors of designated orphan drugs to design and implement treatment protocols to permit treatment of any patient with the rare disease or condition during investigations of the drug upon request by the patient’s physician.” Proposed Regulations, *supra* note 9, at 3344. See also 21 C.F.R. § 316.40 (1999) (“Prospective investigators seeking to obtain treatment use of designated orphan drug may do so as provided in [21 C.F.R.] § 312.34”); Veronica Henry, *Problems with Pharmaceutical Regulation in the United States: Drug Lag and Orphan Drugs*, 14 J. LEGAL MED. 617, 624 (1993).

C. Orphan Drug Market Exclusivity in Biotechnology Business Strategy

One of the greatest challenges for the emerging biotechnology company and its legal counsel is to integrate its intellectual property and regulatory strategies with its financial plan.⁵⁰ After discovering a new compound that may have beneficial medical properties, a company typically applies for a patent, since patent protection precludes other companies from selling or obtaining a patent on the compound.⁵¹ "The biotechnology industry relies heavily on adequate patent protection to recoup the costs of bringing new drugs to the market and to persuade investors to provide the necessary capital to the industry."⁵²

Congress had expected that the Orphan Drug Act would be used primarily by sponsors' orphan drugs that did not qualify for product or composition of matter patents.⁵³ Indeed, one of the most powerful and widely used applications of biotechnology is to enable the production of commercially viable quantities of otherwise rare or very difficult to produce compounds, the prior knowledge of which may preclude composition of matter patent protection. Recombinant Human Growth Hormone, the subject of the first Orphan Drug Act dispute, was precisely such a drug. However, Orphan Drug exclusivity can still be of significant value even where a compound is also the subject of a patent. A patent for a compound is likely to be issued well before the compound receives FDA approval.⁵⁴ Thus, the patent holder's monopoly marketing

50. See Robert A. Bohrer, *Foreward: Biotechnology Business Strategy: A Lawyer's Perspective*, 33 CAL. W. L. REV. 1, 6 (1996).

51. See 35 U.S.C. § 271 (1994) (infringement of patent).

52. 141 CONG. REC. S15221 (daily ed. Oct. 17, 1995) (statement of Sen. Hatch).

53. See *Genentech, Inc. v. Bowen*, 676 F. Supp. 301, 304-05 (D.D.C. 1987).

As originally enacted, the Act limited the availability of exclusive marketing rights to drugs "for which a United States Letter of Patent may not be issued" In considering the proposed legislation, the House Committee on Energy and Commerce found that many potential orphan drugs are not patentable, and stated: "In order to provide some incentive for the development of these particular orphan drugs, the Committee's bill includes an exclusive marketing right for the sponsor of such a drug." Thus, the exclusivity provision of the Act was designed to complement the patent laws, filling gaps that might leave orphan drug manufacturers unprotected.

Id. at 304 (citations omitted).

54. Patents are generally issued within three years of application; however, the prosecution of an application may take much longer than that in some cases. See, e.g., *In re Ochiai*, 71 F.3d 1565, 1566 (Fed. Cir. 1995) (seventeen years from filing of parent

period may be significantly less than the statutory twenty years from the filing date of the patent application.⁵⁵ The patent term is running during the more than seven years⁵⁶ it takes to perform the pre-clinical and clinical tests required to obtain FDA approval for the average new drug application.⁵⁷ The FDA approval process consumes one-third to one-half of the patent term for an average product, substantially reducing the likelihood that an inventor will recover investment costs.⁵⁸ The lag

application to final rejection by the PTO and three more years for appeal which allowed the patent to issue); *In re Brana*, 51 F.3d 1560, 1562 & n.2 (Fed. Cir. 1995) (eight years from application to appeals court decision reversing PTO rejection); *Chiron Corp. v. Abbott Lab.*, 902 F. Supp. 1103, 1109 (N.D. Cal. 1995) (eight years from filing to issuance); see also Mark A. Hurwitz & Richard E. Caves, *Persuasion or Information? Promotion and the Shares of Brand Name and Generic Pharmaceuticals*, 31 J.L. & ECON. 299, 301 (1988) (suggesting that the effective patent protection period was approximately half of the then 17-year protection period); Alan D. Lourie, *Patent Term Restoration: History, Summary, and Appraisal*, 40 FOOD DRUG COSM. L.J. 351, 352 (1985); Mark A. Hurwitz & Richard E. Caves, *Persuasion or Information? Promotion and the Shares of Brand Name and Generic Pharmaceuticals*, 31 J.L. & ECON. 299, 301 (1988) (stating that during the time period for their study, the effective patent protection period was about half of its then 17-year protection period). But see Bruce Lehman, *Major Biotechnology Issues for the U.S. Patent and Trademark Office*, 33 CAL. W. L. REV. 49, 53 (1996) (stating that average pendency of applications from filing to issue down to 19.1 months).

55. See 35 U.S.C. § 154(a)(2) (1994).

56. See Alan D. Lourie, *A Review of Recent Patent Term Extension Data*, 71 J. PAT. OFF. SOC'Y 171, 174 (1989) (surveying time required to perform clinical testing and obtain FDA approval for sixty-five patented human pharmaceuticals).

57. In an attempt to partially remedy this problem, Congress passed 35 U.S.C. § 156(c)(2) and 156(d)(5)(F)(i) as part of the Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 1984 U.S.C.C.A.N. (98 Stat.) 1585 (codified as amended in scattered sections of 21 U.S.C. and 35 U.S.C.). This Act also "expands the number of drugs suitable for an abbreviated new drug application [("ANDA")." Dixie Farley, *Benefit vs. Risk: How FDA Approves New Drugs*, in FROM TEST TUBE TO PATIENT, *supra* note 7, 256 PLI/PAT. 164, 174. "ANDAs make it less costly and time-consuming for generics, which are often sold at lower prices than brand-name drugs, to reach the market." *Id.* Thus, once an ANDA for a drug is approved, the innovator's profits are greatly reduced. This Act seeks to balance the benefits of lower-priced ANDAs with the necessary incentives for drug innovation. "'Patent Term Restoration' refers to the [then seventeen] years of legal protection given a firm for each drug patent. Some of that time allowance is used while the drug goes through the approval process, so this law allows restoration [of one-half of the time which elapses from the initiation of clinical trials until market approval with a maximum restoration of five years, regardless of how much time actually elapsed or how much of the patent term remains]." *Id.*

58. See Susan Kopp Keyack, Note, *The Drug Price Competition and Patent Term Restoration Act of 1984: Is it a Healthy Long Term Solution?*, 21 RUTGERS L.J. 147, 150-55 (1989) (reviewing the negative effect on the introduction of pioneer drugs of the

between patent filing and FDA approval raises the value of the Orphan Drug period of market exclusivity, which does not begin until FDA approval.⁵⁹

The Orphan Drug Act thus provides incentives for biotechnology companies in the intersecting concerns of intellectual property protection and rapid drug approval. In a biopharmaceutical development strategy, it is important to get into the marketplace sooner, with a longer patent term remaining. This is important enough that it influences, if not dictates, the choice of initial target indication for a biotechnology company's lead compound.⁶⁰ As long as the time period necessary for gaining product approval effectively consumes a substantial portion of a drug's patent-life, the Orphan Drug Act will continue to be a central part of many biotechnology companies' product development strategies.⁶¹

D. The Effect of the Orphan Drug Act on Drug Innovation

Pharmaceutical manufacturers have long argued that the Orphan Drug Act procedures do not provide sufficient certainty to guide their R&D investments. One source of such uncertainty is inherent in the potential competition among sponsors of the same or similar orphan drug. Although two sponsors of the same drug may receive orphan drug designation during the development phase, the seven-year marketing exclusivity is awarded solely to the first company to achieve market approval for the drug.⁶² Thus, a company may be the first to conceive of an orphan drug program⁶³ and invest resources into pre-clinical and

increased regulatory review period following the 1962 amendments to the FFDCA).

59. See H.R. REP. NO. 99-153, *reprinted in* 1985 U.S.C.C.A.N. 301, 302-06 (concerning the 1985 Amendments to the Orphan Drug Act which extended orphan drug protection to qualifying drugs even if they were patented). "The Orphan Drug Act therefore provides additional market exclusivity . . . as an incentive for developers for whom a patent is insufficient because[] the proposed drug would not be patentable [or] the patent would have expired by the time the drug was ready for market[] or . . . shortly thereafter." Evan Ackiron, *Patents for Critical Pharmaceuticals: The AZT Case*, 17 AM. J.L. & MED. 145, 158 (1991).

60. See Bohrer, *supra* note 50, at 10.

61. See Haffner, *supra* note 6, at 600.

62. See Proposed Regulations, *supra* note 9, at 3341 ("This interpretation means that other applicants, who may have invested substantial money and effort in supporting their applications, are barred from marketing for the 7-year period of exclusivity even though they filed before or shortly after the applicant whose product was approved."); see also Clissold, *supra* note 4, at 134.

63. An example of such a program is the development of interferon β in the treatment for multiple sclerosis ("MS") discussed *infra* Part V.

clinical research, only to lose that investment if another company is the first to receive drug approval for that orphan drug.⁶⁴ Because the application for orphan designation is kept secret until FDA approval,⁶⁵ and because companies may not apply for orphan drug designation until clinical trials have started, a company may not realize that it is in a race with another company for orphan drug approval.⁶⁶ In a situation in which two companies are developing an orphan drug, if neither company knows which one is ahead in drug testing, both companies may continue competing in hopes of recovering their investment.⁶⁷ Such competition over an orphan drug is unproductive, particularly in a market that is by definition unprofitable.⁶⁸

Although the uncertainty of a race to develop a product undermines the goal of encouraging innovation,⁶⁹ such uncertainty may be unavoidable. Of course, the risk of being beaten to the marketplace is quite different from the risk of being first to market only to find that

64. *Berlex Lab., Inc. v. FDA*, 942 F. Supp. 19 (D.D.C. 1996), *see infra* Part V, presents a slight variation on this point. Interferons are known to be potent modulators of the immune system, and it would be reasonably obvious to try interferon β in a wide range of auto-immune diseases where clinical benefit might be derived from dampening the body's immune response. MS is one such disease, and thus it is not surprising that more than one developer of interferon β would seek orphan drug approval for its use in MS.

65. *See* 21 C.F.R. § 316.52(a) (1999).

[21 C.F.R.] § 316.52(a) provides that no information submitted by a sponsor as part of a request for orphan-drug designation would be released by FDA to the public prior to such time as FDA takes final action on the request. This means that unless previously disclosed or acknowledged, FDA would not make public the existence of any pending orphan-drug designation request.

Proposed Regulations, *supra* note 9, at 3344. Further, "FDA will not provide any materials which it is obligated to treat as trade secret or confidential." Orphan Drug Regulations, 57 Fed. Reg. 62,076, 62,081 (1992) (to be codified at 21 C.F.R. pt. 316) [hereinafter Final Regulations].

66. *See* Rin-Laures & Janofsky, *supra* note 39, at 294. As a practical matter, however, biotechnology companies tend to need to publicize their development projects in order to attract investors, thus reducing the uncertainty by making it likely that competitors would be aware of the fact of competition. *See* Michael J. Malinowski & Maureen A. O'Rourke, *A False Start? The Impact of Federal Policy on the Genotechnology Industry*, 13 YALE J. ON REG. 163, 177-78 (1996) (explaining the financial pressures faced by biotechnology companies).

67. *See* Rin-Laures & Janofsky, *supra* note 39, at 294.

68. *See id.*

69. *Cf.* *United Carbon Co. v. Binney & Smith Co.*, 317 U.S. 228, 236 (1942) ("A zone of uncertainty which enterprise and experimentation may enter only at the risk of infringement claims would discourage invention only a little less than unequivocal foreclosure of the field.").

winning the race provided no real victory at all.⁷⁰ Despite the perceived uncertainty, the Orphan Drug Act has been successful in bringing many orphan drugs to market, with more new drugs undergoing R&D.⁷¹ The Orphan Drug Act has been successful enough to inspire imitation in other countries.⁷²

One reason for this success is that most orphan drugs have been developed by small biotechnology companies.⁷³ For small biotechnology companies, demonstrating to investors the ability to successfully develop any product is a significant corporate milestone.⁷⁴ Also, while diseases affecting 200,000 Americans are “rare” under the law, they may represent sizeable — even hugely profitable — markets for small companies. In addition, the orphan drug designation is based on U.S. disease populations and does not account for the potential profits on international sales — a key target for both large pharmaceutical companies and biotechnology companies.⁷⁵ Another reason for the success of the Orphan Drug Act in bringing orphan drugs to market is that drugs developed for a rare disorder may also work on more common diseases. For example, the biotechnology company Genentech originally developed human growth hormone (hGH) to treat children with hypopituitary dwarfism, but hGH is also useful in treating other growth deficiencies.⁷⁶ Such extremely successful orphans, like human

70. See *infra* Part IV on the recent battle between Berlex and Biogen.

71. See JOHN HENKEL, ORPHAN DRUG PRODUCTS: NEW HOPE FOR PEOPLE WITH RARE DISORDERS, FDA SPECIAL REPORT ON NEW DRUG DEVELOPMENT IN THE UNITED STATES (1995), available at <<http://www.fda.gov/fdac/special/newdrug/orphan.html>> (“Today, new orphan products come on the market regularly. Some companies have even sprung up to develop and market orphan drugs exclusively. By 1995, the FDA had approved 108 orphan products, a number some say will at least double in the next decade.”); see also Victoria Griffith, *Orphans’ Home*, FIN. TIMES, Nov. 21, 1996, at 22 (“A number of treatments are nothing short of miraculous for some patients.” (quoting Abbey Meyers, President of the National Organization for Rare Disorders)); Marjorie Shaffer, *1996 Banner Year for Biotech Drug Oks; Some Say Industry’s Best Ever*, BIOTECHNOLOGY NEWSWATCH, Jan. 20, 1997, available in 1997 WL 8790304.

72. See Cavalier, *supra* note 4, at 448; see also Rin-Laures & Janofsky, *supra* note 39, at 270 n.6.

73. See Griffith, *supra* note 71, at 22 (“Treatments for malaria, leprosy, and African sleeping sickness have all been developed under the Orphan Drug Act over the past decade. These treatments are based in biotechnology, rather than the traditional medical chemical technologies of the major pharmaceutical companies.”).

74. See HENKEL, *supra* note 71 (“Large firms need exclusivity to convince management to invest capital. Small-to-medium-sized companies need it to ensure stockholders that the product won’t be infringed upon by competitors.”).

75. See Griffith, *supra* note 71, at 22.

76. See *id.* One way to broaden the scope of the Orphan Drug Act is by dividing the FDA-approved indications for a given product to its smallest possible market. For

growth hormone and erythropoietin (EPO), are "blockbuster drugs" and arguably do not need the protections provided by the Orphan Drug Act.⁷⁷ Both hGH and EPO were the subject of major battles over the scope of Orphan Drug Act protection.⁷⁸

Critics of the Orphan Drug Act, spurred by such instances of enormously profitable orphan drugs, have expressed two very different concerns. First, these critics decry the fact that market exclusivity leads to higher prices that prohibit access to the drug.⁷⁹ Second, apparently believing that only minimal commercial incentives are justified, the critics assert that profitable orphan drugs violate the spirit behind the Orphan Drug Act.⁸⁰ These criticisms led to an amendment to the Orphan

example, hGH has received orphan status designation for several growth deficiencies by four different sponsors. See Jess G. Thoene, *Curing the Orphan Drug Act*, 251 SCI. 1158 (1991).

77. See Amy E. Carroll, Comment, *Not Always the Best Medicine: Biotechnology and the Global Impact of U.S. Patent Law*, 44 AM. U. L. REV. 2433, 2487 n.388; John J. Flynn, *The Orphan Drug Act: An Unconstitutional Exercise of the Patent Power*, 1992 UTAH L. REV. 389, 396-400 (1992); Veronica Henry, *Problems with Pharmaceutical Regulation in the United States: Drug Lag and Orphan Drugs*, 14 J. LEGAL MED. 617, 635 (1993); Larry Thompson, *The High Cost of Rare Diseases: When Patients Can't Afford to Buy Lifesaving Drugs*, WASH. POST, June 25, 1991, at Z10.

Although it is illegal for a manufacturer to promote a drug for treatment of a condition for which the FDA has not approved it, there are no constraints on physicians' use of approved drugs. Once a drug is on the market, physicians may prescribe it for any condition that, in their judgment, appears indicated.

Thoene, *supra* note 76, at 1158. Such uses are known as "off-label." Thus, even though its market exclusivity is for a limited indication, a product may enjoy a much wider market. See *id.* Of course, the wider market created by off-label uses is a double-edged sword. If another manufacturer receives approval for a non-orphan indication for an orphan drug, then physicians may also prescribe the non-orphan labeled version of the drug for patients in the orphan drug population.

78. See *infra* Parts IV.A-B.

79. See, e.g., *Orphan Drug Reauthorization: Hearing Before the Subcomm. on Health and the Environment of the Comm. on Energy and Commerce of the House of Representatives on H.R. 4160*, 103d Cong., 2d Sess. 1 (1994); *Anticompetitive Abuse of the Orphan Drug Act: Invitation to High Prices: Hearings Before the Subcomm. on Antitrust, Monopolies and Business Rights of the Senate Judiciary Comm.*, 102d Cong., 2d Sess. 198 (1992); Flynn, *supra* note 77, at 396-400; Thompson, *supra* note 77, at Z10; John Carey & Joan O. Hamilton, *These "Orphans" Don't Need Any Nurturing*, BUS. WK., July 2, 1990, at 38; Ann Gibbons, *Billion-Dollar Orphans: Prescription for Trouble*, 248 SCIENCE 678 (1990).

80. See Janice Marchiafava Hogan, Note, *Revamping the Orphan Drug Act: Potential Impact on the World Pharmaceutical Market*, 26 LAW & POL'Y INT'L BUS. 523, 531-33 (1995) (arguing that the "monopoly prices" for pharmaceuticals will not be paid by health insurance or government assistance programs).

Drug Act in 1990 to permit simultaneous licensing of the same orphan drug for the same rare disease under some circumstances.⁸¹ The amendment was passed by both houses of Congress, but President George Bush “pocket vetoed” it because he believed that the bill would weaken “the marketing incentives provided by the Act.”⁸²

Those who see the marketing exclusivity as a surrogate for patent protection refer to the extension of patent-like exclusivity by orphan status as “evergreening.”⁸³ However, the Orphan Drug Act differs from patent protection because it provides incentives that are specifically focused on the problems of drug development, particularly for smaller patient populations. Unless the important unmet needs of orphan disease sufferers can be met in some other way, the potential incentives of the Orphan Drug Act will continue to be essential to providing new therapies for those patients.

III. THE SCIENTIFIC CONTEXT OF THE PROBLEM OF DISTINGUISHING SIMILAR DRUGS

Since the 1985–1986 battle over two versions of recombinant Human Growth Hormone,⁸⁴ the FDA has been repeatedly confronted with a continuing problem with the Orphan Drug Act — the “same vs. different” problem. If the FDA considers two structurally very similar drug variants to be “different,” it may approve both drugs. When “same vs. different” is narrowly construed in this manner, an orphan drug’s market exclusivity is thereby narrowed and the incentives to develop such orphan drugs are substantially diminished by the risk that a second manufacturer could enter the market with a similar — almost copycat — variation.⁸⁵ This is especially problematic for biotechnology companies, because while the R&D costs to bring a drug to market are high, it is

81. See H.R. 4638, 101st Cong., 2d Sess., 136 CONG. REC. H5799 (daily ed. July 30, 1990). The amendment would have permitted simultaneous licensing of the same orphan product for the same indication if (i) the second company requests orphan designation within 6 months of publication by the FDA of its action to designate the drug for the first company; (ii) the second company initiates human clinical trials not more than 12 months after the first company initiated clinical trials; and (iii) the second company submits an approvable new drug application to the FDA no more than one year after the first company submits its new drug application. See *id.*

82. Memorandum of Disapproval for the Orphan Drug Amendments of 1990, 26 WEEKLY COMP. PRES. DOC. 1796 (Nov. 8, 1990), 137 CONG. REC. H73 (daily ed. Jan. 3, 1991).

83. See Haffner, *supra* note 6, at 599.

84. See *infra* Part IV.A.

85. Cavalier, *supra* note 4, at 450.

relatively easy to make minor changes in genes and proteins that are unlikely to have pharmacological significance.⁸⁶ On the other hand, some seemingly minor sequence changes may result in significant differences in protein activity.⁸⁷

The problem for the FDA in defining sameness under the Orphan Drug Act would seem to be to distinguish between significant and insignificant changes in a way that provides as much guidance and clarity as possible for companies that are considering the development of orphan drugs. Before the development of recombinant proteins by the biotechnology industry — when smaller, simpler chemical structures provided the basis for most drugs — two drugs were considered the same if they had the same active moiety.⁸⁸ This strict structural approach worked well because even slight changes in the chemical structure of the active moiety are reasonably likely to result in significant pharmacologic differences for small molecules produced by chemical syntheses. However, the FDA's definition of sameness does not work well for large biological molecules since slight structural variations in such molecules often do not result in pharmacologic differences.⁸⁹ With the growth of the biotechnology industry, an increasingly large percentage of designated orphan drugs are proteins or other large biological molecules.⁹⁰

Among the biotechnology products are genes, proteins, or glycoproteins. All living organisms contain genes, which consist of DNA (deoxyribonucleic acid). DNA is made up of varying sequences of "nucleotides," which are arranged in a DNA molecule like beads on a string. The specific arrangement of the nucleotides is a "DNA sequence." Only four nucleotides comprise DNA,⁹¹ but a single strand

86. For a general description of the problem of minor variations in biotechnology inventions, see Brief of Amicus Curiae Chiron Corp. in Support of Respondent at 14–18, *Warner-Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17 (1997), available in 1996 WL 254689 [hereinafter Chiron Brief].

87. See *id.* at 16–17.

88. See Proposed Regulations, *supra* note 9, at 3341; see also 21 C.F.R. § 316.3(b)(2) (1999) ("Active moiety means the molecule or ion . . . responsible for the physiological or pharmacological action of the drug substance.").

89. See Joseph A. Levitt & John V. Kelsey, *The Orphan Drug Regulations and Related Issues*, 48 FOOD & DRUG L.J. 525, 527 (1993); see also Brief of Biotechnology Industry Organization as Amicus Curiae in Support of Respondent at 9, *Warner-Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17 (1997), available in 1996 WL 249509 [hereinafter BIO Brief].

90. See Levitt & Kelsey, *supra* note 89, at 527.

91. These four are Adenine (A), Thymine (T), Cytosine (C), and Guanine (G). See BIO Brief, *supra* note 89, at 8 n.4

of DNA may have thousands or millions of nucleotides. DNA encodes the information that living cells use to build proteins.

Proteins perform many functions in living organisms — “from digesting food to forming muscles to helping the immune system combat infections”⁹² — and have been the leading drug products produced by the biotechnology industry.⁹³ A protein is made up of varying sequences of “amino acids,” some of which may have carbohydrate molecules attached.⁹⁴ The arrangement of amino acids is a “protein sequence.” A specific DNA grouping of three nucleotides, a “codon,” encodes a single amino acid.⁹⁵ There are sixty-four possible codons (4^3), with sixty-one of these encoding amino acids.⁹⁶ Since there are only twenty naturally occurring amino acids,⁹⁷ several different codons may encode the same amino acid,⁹⁸ while a few codons are “unique” so that the encoded amino acid is encoded by one and only one codon.⁹⁹

The process whereby proteins are constructed from the information in the DNA codons is called “translation.” Translation of each codon into its corresponding amino acid yields the protein’s primary structure, which is the linear sequence of amino acids in the protein. After the amino acid chain of the protein is completed, any additional modifications to the protein are referred to as “post-translational.” Post-translational changes include the enzymatic attachment of various side-groups, such as saccharides, which determine the protein’s secondary structure, and the folding of the linear protein into a complex three-dimensional shape, which is referred to as its tertiary structure.¹⁰⁰

Without a careful, functional definition of “sameness,” any market exclusivity for a gene could be completely valueless, because

92. Chiron Brief, *supra* note 86, at 15.

93. *GI Goes Fishing*, IN VIVO THE BUSINESS & MEDICINE REPORT, October 1996, at 17 (available on Lexis).

94. The attachment of carbohydrates to a protein is known as glycosylation and the resulting protein is a glycoprotein. *See infra* text following note 102.

95. *See* BIO Brief, *supra* note 89, at 8.

96. *See id.* at 8.

97. They are Alanine, Cysteine, Aspartic Acid, Glutamic Acid, Phenylalanine, Glycine, Histidine, Isoleucine, Leucine, Lysine, Methionine, Asparagine, Proline, Glutamine, Arginine, Serine, Threonine, Valine, Tryptophan, and Tyrosine. *See id.* at 8 n.3.

98. For example, the codons GCA, GCC, GCG and GCT each encode the amino acid Alanine. *See id.* at 8.

99. *See* BRUCE ALBERTS ET AL., MOLECULAR BIOLOGY OF THE CELL 102–03 (3d ed. 1994).

100. For two overviews of this area of basic molecular biology, see ALBERTS ET AL., *supra* note 99, at 589–94, 604–09, 628–29 and HARVEY LODISH ET AL., MOLECULAR CELL BIOLOGY 694–722 (3d ed. 1995).

competitors can easily substitute nucleotides to create a “different” gene coding for an identical protein.¹⁰¹ Proteins present a similar problem, because certain individual amino acids are generally structurally interchangeable (because of their similar basic structure and net charge) without producing a noticeable functional effect. As the Federal Circuit noted in analyzing EPO (a drug that has received Orphan Drug Act protection), “over 3,600 different EPO analogs can be made by substituting at only a single amino acid position, and over a million different analogs can be made by substituting three amino acids.”¹⁰² Many analogs are functionally indistinguishable, so distinguishing among the analogs serves no purpose.

The problem of insignificant variation is even greater for glycoproteins. Glycoproteins are proteins with covalently-bonded carbohydrate (sugar or saccharide) groups. The saccharide portion is attached to the protein post-translationally and enzymatically, rather than being genetically determined like the protein structure. Different species of animals add different saccharides to the same kind of protein. Even different cell lines of the same species and different cells in the same body can add different saccharides to the same kind of protein. Thus, when recombinant proteins are made by inserting the same gene sequence in different organisms — such as *Escherichia coli* (*E. coli*), yeast, and Chinese hamster ovary (CHO) cells — the resulting proteins will be glycosylated differently but may nevertheless have the same biological activity. Whether or not such differences in glycosylation will result in differences in biological activity is not currently predictable.

For a company pursuing the very costly development of a gene-, protein-, or glycoprotein-based drug, the problem of predicting intellectual property protection against competitors’ variant drugs is a major concern.

101. See *In re Bell*, 991 F.2d 781, 784 (Fed. Cir. 1993) (noting that 10^{36} possible nucleotide sequences could encode a protein drug called insulin-like growth factor (IGF)). Although no drugs have yet been approved which consist exclusively or primarily of a DNA sequence, several companies are working to develop DNA constructs as therapeutics. See e.g., Vical Incorporated News Release, *Vical Licenses “Naked” DNA Technology to Centocor for Therapeutic Cancer Vaccines* (Feb. 11, 1998) <http://www.vical.com/html/nr_980211.html>.

102. *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1213 (Fed. Cir. 1991).

IV. A BRIEF HISTORY OF THE SAME VERSUS DIFFERENT PROBLEM UNDER THE ORPHAN DRUG ACT

A. Human Growth Hormone

Almost from the start, the Orphan Drug Act has been dogged by major controversy over whether two competing products were the same or, alternately, sufficiently different to allow the second product to be approved for the same indication. The Act's definition of a "different" drug¹⁰³ was the issue in litigation over the orphan drug designation for hGH.¹⁰⁴ hGH is a protein secreted by the human pituitary gland that can strongly affect height. Administration of this hormone can restore growth in children with hypopituitary dwarfism.

Genentech developed, with the assistance of orphan designation funding, a genetically-engineered human growth hormone and was granted market exclusivity for this hormone, Protropin.¹⁰⁵ Protropin was a key product in Genentech's success as a biotechnology company.¹⁰⁶ Eight months later, the FDA granted Eli Lilly & Co. orphan drug market exclusivity for a human growth hormone that differed by only a single amino acid.¹⁰⁷ Genentech's Protropin had an additional amino acid that Lilly's human growth hormone (Humatrope) lacked. From a medical and clinical standpoint, there was no difference in safety and efficacy between Genentech's Protropin and Lilly's Humatrope.¹⁰⁸

Genentech filed a citizen petition¹⁰⁹ to dissuade the FDA from approving Humatrope, claiming "that Lilly's drug was, for the purposes

103. See Rin-Laures & Janofsky, *supra* note 39, at 289.

104. See *Genentech, Inc. v. Bowen*, 676 F. Supp. 301, 306 (D.D.C. 1987).

105. See *id.* at 306.

In terms of chemical structure, Genentech's [recombinant] hGH has the same sequence of 191 amino acids found in hGH, with an additional methionine amino acid group attached to one end of the molecule. Because Genentech's drug apparently does not present the risk of Creutzfeldt-Jakob Disease associated with pituitary-derived hGH, its approval in 1985 filled an important health need.

Id.

106. See *id.* ("Genentech estimates that it invested approximately \$45 million developing its [recombinant] hGH product.").

107. See *id.*

108. See *Novo Nordisk of N. Am., Inc. v. Genentech, Inc.*, No. 94 Civ. 8634 (CBM), 1995 WL 512171, at *18 (S.D.N.Y. Aug. 28, 1995), *vacated*, 77 F.3d 1364 (Fed. Cir. 1996).

109. Any interested person can initiate administrative proceedings by petitioning the Commissioner of the FDA to take, to refrain from taking, or to reconsider an action. See 21 C.F.R. §§ 10.25, 10.30, 10.33, 10.35 (1999).

of the Orphan Drug Act, the same as Protropin and therefore ineligible for marketing approval"¹¹⁰ When the FDA granted Lilly approval and market exclusivity for Humatrope, Genentech sought a temporary injunction.¹¹¹

The U.S. District Court for the District of Columbia held that the two human growth hormones were not the "same" drug under the Orphan Drug Act, but it explicitly declined to provide any "universal rule for determining whether two drugs are 'different' [under the Act]. That responsibility is statutorily imposed on the FDA. Until the FDA endeavors to meet that obligation, the courts will be forced to make case-by-case determinations based on the broad policies embodied in the Act."¹¹²

B. Erythropoietin

The protein erythropoietin was also the subject of a "same vs. different" orphan drug controversy, in the highly competitive, high-stakes race to clone the gene for the human hormone.¹¹³ EPO is a glycoprotein that stimulates red blood cell production, which is useful in the treatment of anemia. "[T]he commercial availability of manufactured EPO to those suffering from a variety of diseases is invaluable."¹¹⁴ Erythropoietin was a key product in Amgen's success as a biotechnology company.

In 1989, Amgen received orphan drug marketing exclusivity for its EPO product Epogen, for the treatment of the chronic anemia associated with end-stage renal disease—a "rare disease."¹¹⁵ Seeking access to the market, Chugai and its marketing partner Genetics Institute tried to obtain orphan drug status for their erythropoietin product, Marogen,¹¹⁶ arguing that because the Marogen glycosylation pattern differed from Amgen's Epogen, Marogen should not be blocked from the market.¹¹⁷

110. *Genentech*, 676 F. Supp. at 307.

111. *See id.*

112. *Id.* at 313.

113. Several biotechnology companies had tried to clone the EPO gene. "[Biogen] began its EPO project at the end of 1981, and continued it as a full-scale project until March, 1985, when the project was 'officially terminated.'" *Amgen, Inc. v. Chugai Pharm. Co.*, 13 U.S.P.Q.2d (BNA) 1737, 1752 (D. Mass. 1989) ("Amgen I"), *aff'd in part, rev'd in part, vacated in part*, 927 F.2d 1200 (Fed. Cir. 1991) ("Amgen II").

114. *Ortho Pharm. Corp. v. Amgen, Inc.*, 709 F. Supp. 504, 505 (D.Del. 1989).

115. *See* Donna K.H. Walters, *Two Proposed Laws Bitterly Divide Biotech Industry Drugs*, L.A. TIMES, June 3, 1990, at D1.

116. *See id.*

117. *See* Levitt & Kelsey, *supra* note 89, at 526. Chugai and Genetics Institute also

Eventually, the FDA denied the Chugai/Genetics Institute application.¹¹⁸ The battle over EPO continued, however, until Chugai and Genetics Institute lost a patent dispute with Amgen, leaving Amgen in exclusive control of the protein.¹¹⁹

C. The FDA Orphan Drug Regulations: An Early Response

These cases prompted the FDA to address the “important, but politically tiresome, details”¹²⁰ and promulgate regulations to define “sameness” under the Orphan Drug Act.¹²¹ The FDA Orphan Drug regulations tried “to ensure both that improved therapies will always be marketable and that orphan drug exclusivity does not preclude significant improvements in treating rare diseases.”¹²² To be considered different under the Orphan Drug Act, small molecule drugs cannot have the same “active moiety,”¹²³ while large biological drugs cannot contain the “same principal molecular structure.”¹²⁴ Because so much promising

filed citizen petitions challenging the orphan drug status of Epogen, on the grounds that its affected population was larger than 200,000 and that the drug received different approval and market exclusivity indications than Amgen had requested. Chugai further asserted that Amgen did not inform the FDA of a court’s ruling that Amgen had infringed the ’195 patent. *See Amgen I*, 13 U.S.P.Q.2d at 1740.

118. *See* Edmund L. Andrews, *Kidney Drug Setback for Genetics Institute*, N.Y. TIMES, Jan. 15, 1991, at D4.

119. *See Amgen II*, 927 F.2d 1200 (Fed. Cir. 1991).

120. *Genentech, Inc. v. Bowen*, 676 F. Supp. 301, 312 (D.D.C. 1987).

121. *See Cavalier, supra* note 4, at 450.

122. Proposed Regulations, *supra* note 9, at 3338.

123. *See* 21 C.F.R. § 316.3(b)(2) (1999) (“Active moiety means the molecule or ion . . . responsible for the physiological or pharmacological action of the drug substance.”).

124. *See* 21 C.F.R. § 316.3(b)(13)(ii) (1999).

Same drug means . . . [i]f it is a drug composed of large molecules (macromolecules), a drug that contains the same principal molecular structural features (but not necessarily all of the same structural features) and is intended for the same use as a previously approved drug, except that, if the subsequent drug can be shown to be clinically superior, it will not be considered to be the same drug. This criterion will be applied as follows to different kinds of macromolecules:

(A) Two protein drugs would be considered the same if the only differences in structure between them were due to post-translational events or infidelity of translation or transcription or were minor differences in amino acid sequence; other potentially important differences, such as different glycosylation patterns or different tertiary structures, would not cause the drugs to be considered different unless the

drug development concerns products produced by biotechnology, the FDA Orphan Drug regulations make a "presumption of sameness" even when differences occur in protein structure¹²⁵ in order to clarify and broaden the incentives for large biological drugs (and to respond to issues raised in the hGH and EPO wars). The FDA believed this broader protection was consistent with congressional intent.¹²⁶

When it proposed the regulations regarding the definition of "different," the FDA also considered three definitions that were logical alternatives to the standard it had settled upon. First, the FDA considered allowing "two drugs [to] be considered different if they had any defined structural differences . . . or had a structure that could not be precisely defined."¹²⁷ This very strict approach to "same" protects a first drug only when the second drug is identical. That approach reduced the degree of protection for biological macromolecules because of the ease with which second applicants could make functionally equivalent variants of the first drug.¹²⁸ Second, the FDA considered whether two drugs should be "different" if they could be shown to have a "defined

differences were shown to be clinically superior.

- (B) Two polysaccharide drugs would be considered the same if they had identical saccharide repeating units, even if the number of units were to vary and even if there were postpolymerization modifications, unless the subsequent drug could be shown to be clinically superior.
- (C) Two polynucleotide drugs consisting of two or more distinct nucleotides would be considered the same if they had an identical sequence of purine and pyrimidine bases (or their derivatives) bound to an identical sugar backbone (ribose, deoxyribose, or modifications of these sugars), unless the subsequent drug were shown to be clinically superior.
- (D) Closely related, complex partly definable drugs with similar therapeutic intent, such as two live viral vaccines for the same indication, would be considered the same unless the subsequent drug was shown to be clinically superior.

Id.

125. See Proposed Regulations, *supra* note 9, at 3342–43 ("This criterion makes a presumption of sameness, even in the case of proteins, in the face of minor differences in structure other than differences in the primary amino acid sequence if those differences occur after the basic amino acid change is translated from the RNA. Sameness is also presumed even in the face of amino acid sequence differences if they are 'minor'.").

126. See Final Regulations, *supra* note 65, at 62,079–80 (1992) (rejecting alternatives where "most macromolecules would be ineligible for exclusive marketing rights, an outcome that . . . does not seem compatible with the purpose of the Orphan Drug Act."). See also Levitt & Kelsey, *supra* note 89, at 527.

127. Proposed Regulations, *supra* note 9, at 3342.

128. See *supra* Part III.

structural difference,” but not “simply because of uncertainty about their precise structure or because the drugs are somewhat indeterminate mixtures.”¹²⁹ This alternative also provided “relatively little value to orphan-drug exclusive marketing for macromolecules, allowing any evidence of structural difference, or uncertainty about structure, to cause two drugs to be considered different drugs,”¹³⁰ and provided the opportunity for second sponsors to seek orphan drug approval for minor structural differences.

Third, the FDA considered whether “similar macromolecules would be considered the same unless their structures differed in ways that could reasonably be expected to influence relevant pharmacologic activity. Other structural differences would not cause the second drug to be considered a different drug unless the subsequent drug were shown to be clinically superior.”¹³¹ While the other alternatives clearly provided only a narrow scope of protection for orphan drugs, this alternative might well have provided very broad protection. Like the regulations eventually implemented, this approach makes a “relatively strong presumption of sameness for pharmacologically related drugs,”¹³² but might even more broadly support orphan-drug exclusivity of a first-approved drug in the face of considerable differences in structure in a second drug. However, the FDA decided that this alternative created uncertainty because of the need to make a regulatory judgment as to the probable relationship between structural variations and pharmacological activity, giving too much judgment and discretion to FDA officials. The FDA realized that the regulations did not and could not specify the kinds of structural differences likely to be related to differences in pharmacological activity.¹³³

The FDA’s 1991 Notice of its proposed regulations¹³⁴ provoked numerous comments from the public.¹³⁵ One comment proposed that the concept of “active moiety” should be applied to both macromolecular products and micromolecular products and that the differences in active moieties by themselves should be used as the sole criterion for

129. Proposed Regulations, *supra* note 9, at 3342.

130. *Id.*

131. *Id.*

132. *Id.*

133. *See id.* (“[T]he agency would have to determine that a particular structural change was likely to be associated with a clinical difference without necessarily requiring evidence from clinical studies that it actually did lead to such a difference. This would entail making a complex and potentially controversial judgment.”).

134. *Id.* For a general discussion of this FDA rulemaking, see Rin-Laures & Janofsky, *supra* note 39, at 291–92.

135. *See* Final Regulations, *supra* note 65.

establishing product differences.¹³⁶ The FDA replied that it would be “trivially easy to make minor covalent changes that would leave the activity of the macromolecular drug unaltered, but would create a ‘different drug’”¹³⁷ The FDA added that “[w]hen such a change is meaningful,” however, it deserves exclusive marketing protection.¹³⁸

The final Orphan Drug Act regulations, adopted in 1993, clearly rejected the notion that a macromolecule’s chemical structure should be the principal inquiry in determining whether a second orphan drug application is for the same drug as a prior approved drug.¹³⁹ Rather than basing orphan drug identity on any of the various and problematic structural standards, the FDA decided that a second sponsor should always be able to establish the difference between two similar products based on significant clinical differences.¹⁴⁰ “With regard to macromolecular drugs, clinical superiority by itself will render a subsequent drug different.”¹⁴¹ This “clinical differences” standard was based on the principle that the market exclusivity should not create a barrier to needed patient therapies.¹⁴² “Assuming that a subsequent drug’s marketing application is otherwise approvable, FDA will not interpret the Orphan Drug Act to block approval of any drug proved to be clinically superior to a drug with currently effective exclusive marketing rights.”¹⁴³ In its Orphan Drug Act regulations, the FDA essentially changed the focus from the underlying question of same and different to the question of how the FDA will determine whether a second drug is clinically superior to the first.

The FDA regulations define a “clinically superior” drug as one that “is shown to provide a significant therapeutic advantage over and above that provided by an approved orphan drug”¹⁴⁴ Therapeutic advantage, or clinical superiority,¹⁴⁵ can be shown one of three ways: (1) greater effectiveness; (2) greater safety; or, (3) demonstration that the drug makes a major contribution to patient care in “unusual cases.”¹⁴⁶

136. *See id.* at 62,077.

137. *Id.*

138. *Id.*

139. *See id.* at 62,077, 62,086.

140. *See id.* at 62,086.

141. *Id.* at 62,078.

142. *See Levitt & Kelsey, supra* note 89, at 528–29.

143. Final Regulations, *supra* note 65, at 62,078.

144. *Id.* at 62,086.

145. The terms therapeutic advantage and clinical superiority are interchangeable. Therapeutic advantage is demonstrated when clinical testing of a drug demonstrates it to be superior in an important dimension. *See infra* note 150.

146. *See* 21 C.F.R. § 316.3(b)(3)(i)–(iii) (1999).

To demonstrate greater effectiveness, the same kind of evidence is needed as that generally required to support a comparative effectiveness claim for two different drugs; that is, an improvement as assessed by the drug's "effect on a clinically meaningful endpoint in adequate and well controlled clinical trials."¹⁴⁷ To support a claim of superior safety, the company seeking approval of the second product must establish that its product provides "greater safety in a substantial portion of the target populations, for example, by the elimination of an ingredient or contaminant that is associated with relatively frequent adverse effects."¹⁴⁸ The FDA interpretation is that even "a small demonstrated . . . diminution in adverse reactions may be sufficient to allow a finding of clinical superiority."¹⁴⁹ Finally, a second drug can be considered "clinically superior" if it makes some other "major contribution to patient care."¹⁵⁰ The FDA intends this to be "a narrow category," such as, for example, "the development of an oral dosage form where . . . only a parenteral dosage form" had existed previously.¹⁵¹

The FDA's decision to rely on clinical superiority as the ultimate determinant of whether a second orphan drug was different than a prior, similar drug left the FDA with considerable discretion to decide when head-to-head comparisons of the two drugs would be required to prove clinical superiority. One comment in response to the Orphan Drug regulations suggested that, as proof of clinical superiority, the FDA should always require a demonstration in "rigorous double-blind, head-to-head comparative clinical trials such as those required to support other comparative safety and efficacy claims."¹⁵² Such trials, it was suggested, "should be done using the licensed product and the subsequent product formulated with the same biologically active units"¹⁵³ The FDA

147. 21 C.F.R. § 316.3(b)(3)(i) (1999). *See also* 21 C.F.R. § 201.57(c)(3)(v) (1999); Final Regulations, *supra* note 65, at 62,077.

148. 21 C.F.R. § 316.3(b)(3)(ii) (1999).

149. Final Regulations, *supra* note 65, at 62,078.

150. 21 C.F.R. § 316.3(b)(3)(iii) (1999).

151. Proposed Regulations, *supra* note 9, at 3343. Later suggestions included:

[N]ovel inhalation therapy; oral, intranasal, inhalational, transdermal vehicles of administration where intravenous means were once all that was available; innovative time-release delivery mechanisms; the availability of an improved delivery system that eliminates the risk of hemophilia B; and a new parenteral administration that permits once-a-day administration rather than four-times-a-day injections or infusions.

Final Regulations, *supra* note 65, at 62,079. The FDA replied that "this can only be decided on a case-by-case basis." *Id.*

152. Final Regulations, *supra* note 65, at 62,078.

153. *Id.*

replied that “[w]hile randomized double-blind, concurrently controlled clinical trials are usually the most reliable sources of evidence, other kinds of studies”¹⁵⁴ that demonstrate an improvement as assessed by the drug’s “effect on a clinically meaningful endpoint in adequate and well controlled clinical trials” can be considered to support a finding of clinical superiority.¹⁵⁵ The regulations allow for that possibility even if concurrently controlled trials might ordinarily be required.¹⁵⁶

To summarize the FDA’s regulations on the same and different problem, the general principal is that structurally similar drugs will be considered the same unless the second drug is shown to be clinically superior to the first. Where the issue is efficacy, the situation is quite clear: the only way to show that drug B is more effective than drug A is to directly compare their performance on an important efficacy endpoint.¹⁵⁷ Where the difference is safety or “contribution to patient care,”¹⁵⁸ the guidelines are significantly less clear, as became obvious in the most recent case involving the variant forms of interferon β . If the safety of two drugs is judged on a case-by-case basis, without head-to-head data (because the second drug has a different dosage schedule or route of administration), a second drug sponsor can “play with” the first drug’s data in an effort to produce fewer adverse effects.¹⁵⁹ In defining

154. *Id.*

155. *Id.* at 62,086. *See also* 21 C.F.R. §§ 316.3(b)(3)(i), 201.57(c)(3)(v) (1999).

156. *See* 21 C.F.R. § 314.126 (1999).

157. Although both drugs may be tested at separate times against placebo, each trial would be measuring the effect on the same clinical measure of the disease.

158. Proposed Regulations, *supra* note 9, at 3343.

159. When biotechnology companies plan the clinical development of a new drug, they are necessarily limited by the costs of clinical development as to the number of different doses and routes of administration that will be tested for safety in Phase I. When a pioneer faces what is likely to be a difficult clinical target, such as multiple sclerosis, it is likely that Phase II trials, which are the first trials to look for efficacy in patients with the disease, will use doses at the higher end of the range that is expected to be reasonably safe, in the hopes that those higher doses will produce the desired effect. If efficacy is found in one or more doses in Phase II, the Phase III trials — which test the drug in a greater number of patients, and upon which approval will be based — will likely utilize the Phase II dose that produced the best results. The second applicant thus has the chance to design a Phase II trial that uses the dosage of the first applicant as its highest dose, and can look for efficacy at various fractions of that dose and at different dosage intervals. In *Berlex Laboratories, Inc. v. FDA*, 942 F. Supp. 19 (D.D.C. 1996), the weekly dosage of Avonex, the second drug approved, is less than 10% of the dosage of Betaseron, which is given every other day. Although the ability to have an effect at a lower, less frequent dose may well be due to the very minor differences between the molecules, that is precisely the issue that the FDA did not require directly comparative data to determine. Of course, this general problem does not mean that, in the particular case, Biogen actually gained an advantage from Berlex’s clinical trial —

the Orphan Drug Act's protection for a first-approved drug in terms of clinical superiority, the FDA shifted the focus from molecular structure to biological significance without substantially reducing the real uncertainty that Orphan Drug sponsors face.

V. BETASERON AND AVONEX: THE ORPHAN DRUG ACT'S MOST RECENT CONUNDRUM

The uncertainty in the FDA's guidelines focus on biological significance, and the likelihood that the current guidelines will lead to still more battles over orphan drug exclusivity, was most recently apparent when the FDA decided that interferon β ¹⁶⁰ produced in Chinese hamster ovary ("CHO") cells and interferon β produced in *E. coli* were sufficiently different that both could be approved for the treatment of multiple sclerosis.¹⁶¹ The FDA's decision once again raised substantial

Biogen may simply have done a better job of predicting the necessary dose and designing its own clinical trial.

160. Interferon β is a glycoprotein with one covalently attached carbohydrate. Glycosylation can affect the stability, activity, and half-life of other proteins, but not, as far as is known, interferon β . The carbohydrate is not essential for antigenicity (the characteristic of provoking an immune response), biological activity, or hydrophobicity (affinity for water, a major determinant of a protein's structure and activity). See Ernest Knight, Jr., *Interferon: Purification and Initial Characterization from Human Diploid Cells*, 73 PROC. NAT'L. ACAD. SCI. USA 520, 522 (1976); Tadatsugu Taniguchi et al., *Molecular Cloning of Human Interferon cDNA*, 77 PROC. NAT'L. ACAD. SCI. USA 4003, 4003, 4005 (1980).

161. Multiple sclerosis ("MS") is a chronic, inflammatory disease of the central nervous system, usually striking young adults during the prime of life and economic productivity. MS is the second most common chronic neurologic disease of young adults. About 300,000 Americans have MS and more than 10,000 Americans are diagnosed each year. The disease develops when immune cells attack myelin (the fatty sheath that insulates nerve fibers in the brain and spinal cord) resulting in scar-like tissue (sclerosis) forming in multiple places throughout the central nervous system. This sclerosis destroys the nerves' impulse-conducting ability and leads to the symptoms of MS (weakness, fatigue, loss of coordination, incontinence, numbness and tingling, vertigo, double vision, and speech disturbances). Clinically, MS can be classified into two stages: relapsing-remitting and chronic progressive MS, with approximately 50% of MS patients have the relapsing-remitting form of MS. Most patients start with relapsing-remitting MS, in which exacerbations or "attacks" of neurological symptoms are followed by recovery and attack-free periods of remission. The partial or complete remissions are attributed to the ability of myelin to repair itself. MS patients suffer most during attacks, the timing and duration of which varies, appearing all at once or one at a time. Interferon β decreases the frequency of attacks in relapsing-remitting MS and may slow the progression of the disease by promoting the normal functioning of the immune system, but there is no prevention or cure. Information about MS and interferon β is available from Berlex at <<http://www.betaseron.com>> and from Biogen at

questions about the Orphan Drug Act's market exclusivity incentives for the development of new therapeutics. Berlex Laboratories had received FDA approval to market an E. coli-produced drug — interferon β -1b, whose trade name is Betaseron — as an Orphan Drug for the treatment of relapsing-remitting multiple sclerosis. Berlex felt that the FDA clearly erred when it decided that Biogen's drug — interferon β -1a, whose trade name is Avonex — was sufficiently different to receive approval for the same patient population. Accordingly, Berlex filed a suit against the FDA seeking to have its determination reversed. On October 7, 1996, the U.S. District Court for the District of Columbia dismissed the lawsuit, *Berlex Laboratories, Inc. v. FDA*.¹⁶² The court held the FDA acted lawfully when it determined that Avonex was "clinically superior" to Berlex's Betaseron and that the "FDA's determination that Avonex is safe, pure and potent is amply supported by the record."¹⁶³

The purpose of this Article is not to examine the correctness of the district court's decision to uphold the FDA's determination. The district court's opinion was, and ought to have been, based primarily on considerations of administrative law, particularly the issue of the proper relationship between a court and an administrative agency on a technical matter within the primary competence of the agency.¹⁶⁴ The court did not attempt to decide the "same vs. different" issue underlying the dispute: Are Avonex and Betaseron sufficiently different that Avonex is entitled to be a second entrant into the market for relapsing-remitting multiple sclerosis?¹⁶⁵ Rather, the court reviewed the regularity and sufficiency of the FDA's administrative process.¹⁶⁶ As a decision about administrative law and judicial deference to agency expertise, the decision in *Berlex Laboratories* is unexceptional.

<<http://www.avonex.com>>. See also John J. Alam, *Interferon-beta Treatment of Human Disease*, 6 CURRENT OPINION BIOTECHNOLOGY 688, 688-91 (1995).

162. 942 F. Supp. 19 (D.D.C. 1996).

163. *Id.* at 27.

164. See *id.* at 23-25. "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." *Id.* at 25. For an introduction to these administrative law problems, see ALFRED C. AMAN, JR. & WILLIAM T. MAYTON, *ADMINISTRATIVE LAW* § 13.4 (1993).

165. Rather, the court decided that "[t]he 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. . . . [The FDA's interpretation of that requirement] is entitled to the court's deference." *Berlex Lab.*, 942 F. Supp. at 23.

166. See *id.*

The FDA licensed Betaseron, Berlex's version of interferon β (interferon β -1b), as the first product demonstrated to be effective for treating multiple sclerosis.¹⁶⁷ The FDA had designated Betaseron as an orphan drug on November 11, 1988,¹⁶⁸ and approved the sale of Betaseron to ambulatory patients with relapsing-remitting multiple sclerosis on July 23, 1993.¹⁶⁹ The FDA based the approval on data demonstrating that Betaseron reduced the frequency of exacerbations.¹⁷⁰ On May 17, 1996, however, the FDA approved Avonex (interferon β -1a) for relapsing-remitting multiple sclerosis "to slow the accumulation of physical disability and decrease the frequency of clinical exacerbations."¹⁷¹

In developing Betaseron and Avonex, both Berlex and Biogen, respectively, sought the commercialization incentives provided by the Orphan Drug Act. The potential therapeutic benefits of interferon β had spurred both companies' efforts to produce human interferon β by recombinant DNA procedures. Both Berlex's Betaseron and Biogen's Avonex are produced by such procedures, commonly referred to as biotechnology or genetic engineering. In actual medical practice, the drugs are competitors.¹⁷² The competing drugs each cost approximately \$7,000 for an annual supply;¹⁷³ both are taken by injection. Betaseron is injected under the skin every second day at a dose of 250 μ g per

167. FDA Press Release, *FDA Licenses Interferon Beta-1b* (July 23, 1993) <<http://www.fda.gov/bbs/topics/NEWS/NEW00424.html>>

168. *See id.*

169. *See id.*

170. *See FDA Licenses Interferon Beta-1b, supra* note 167.

171. *Berlex Lab.*, 942 F. Supp. at 22.

172. While it is illegal for a manufacturer to promote a drug for the treatment of a condition not approved by the FDA, physicians are under no such prohibition and may prescribe the drug "off-label" as they deem medically appropriate. *See supra* note 77. Off-label use of interferon β for multiple sclerosis patients is common and seems to be acceptable to experts in the field.

Consensus opinion among multiple sclerosis experts and the [Quality Standards Subcommittee] was that if the drug is effective in reducing the number and severity of exacerbations, . . . then any multiple sclerosis patient who experienced true exacerbations should be able to receive the drug. This would include patients of any age or [Expanded Disability Status Scale or] EDSS level, and patients with relapsing/progressive MS

Practice Advisory on Selection of Patients with Multiple Sclerosis for Treatment with Betaseron: Report of the Quality Standards Subcommittee of the American Academy of Neurology, 44 NEUROLOGY 1537, 1538 (1994).

173. *See* Laurence M. Fisher, *Biotechnology Medications Move Closer to the Market*, N.Y. TIMES, Dec. 24, 1996, at D5.

injection,¹⁷⁴ while Avonex is injected into muscle once a week at a dose of 30 μ g per injection¹⁷⁵ — a difference that may have played a key role in the FDA's approval.¹⁷⁶

Betaseron is produced from a human interferon β -1b gene that has been cloned and expressed in the bacterium *E. coli*. The gene and protein sequence of Betaseron varies from that of the natural molecule by one codon and its corresponding amino acid.¹⁷⁷ Because it is produced in bacteria, Betaseron is not glycosylated. It does, however, have an antiviral activity similar to that of native human interferon β ,¹⁷⁸ thus indicating that glycosylation is probably not essential for full biological activity.

Because FDA's approval of Betaseron was based on data from Berlex's clinical trial involving patients with relapsing-remitting multiple sclerosis¹⁷⁹, the results pertain only to the relapsing-remitting patient group. The trial showed that injection of Betaseron every other day under the skin (subcutaneously) decreased the frequency of flare-ups and kept more patients free of flare-ups over a two-year treatment

174. See Alam, *supra* note 161, at 689; *Interferon-beta-1a Approved for Relapsing Multiple Sclerosis*, MED. SCI. BULL., July 1996, at 5 [hereinafter *Interferon-beta-1a Approved*].

175. See Lawrence D. Jacobs et al., *Intramuscular Interferon Beta-1a for Disease Progression in Relapsing Multiple Sclerosis*, 39 ANNALS NEUROLOGY 285, 285 (1996); *Interferon-beta-1a Approved*, *supra* note 174, at 5; see also The IFNB Multiple Sclerosis Study Group and the University of British Columbia MS/MRI Analysis Group, *Interferon Beta-1b in the Treatment of Multiple Sclerosis: Final Outcome of the Randomized Controlled Trial*, 45 NEUROLOGY 1277, 1277 (1995) [hereinafter 1995 IFNB Study]; The IFNB Multiple Sclerosis Study Group, *Interferon Beta-1b is Effective in Relapsing-Relapsing Multiple Sclerosis: Clinical Results of a Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial*, 43 NEUROLOGY 655, 656 (1993) [hereinafter 1993 IFNB Study]. Biogen's clinical data on the effect of Avonex (interferon β -1a) was sufficient to persuade the FDA to allow its label indication to include the slowing of the progression of physical disability due to the disease as well as the lessening of the frequency of exacerbations, while Berlex' Betaseron clinical data for interferon β -1b only included evidence of its efficacy in reducing the frequency of exacerbations. See *Interferon-beta-1a Approved*, *supra* note 174, at 5.

176. See Michael Smith, *Judge Dismisses Berlex Suit vs. FDA, Ending One MS Drug Battle*, BIOTECHNOLOGY NEWSWATCH, Oct. 21, 1996, at 1; see also *Berlex Lab.*, 942 F. Supp. at 22.

177. See Alam, *supra* note 161, at 688. A serine replaces a cysteine at amino acid position 17. See *id.*

178. See 1995 IFNB Study, *supra* note 175.

179. See *FDA Licenses Interferon Beta-1b*, *supra* note 167.

period.¹⁸⁰ Adverse reactions to Betaseron included flu-like symptoms and inflammation and pain at the injection site.¹⁸¹

Beginning in about 1991, Biogen began to manufacture Avonex, using a different cell line and a different manufacturing process.¹⁸² On May 17, 1996, the FDA approved Avonex for the treatment of active relapsing forms of multiple sclerosis to slow the deterioration of physical ability and decrease the frequency of attacks.¹⁸³ The definition of “active relapsing” multiple sclerosis included patients with both relapsing-remitting and relapsing-progressive forms of the disease¹⁸⁴ — a more diverse population than the one studied by Berlex and approved for Betaseron.

When approving the licensing of Avonex, the FDA relied upon a randomized, double-blind multi-center trial of active relapsing multiple

180. See 1995 IFNB Study, *supra* note 175, at 1278–81; 1993 IFNB Study, *supra* note 175, at 657–60; The IFNB Multiple Sclerosis Study Group, *Interferon beta-1b is Effective in Relapsing-remitting Multiple Sclerosis: MRI Analysis Results of a Multicenter, Randomized, Double Blind, Placebo Controlled Trial*, 43 NEUROLOGY 662 (1993).

181. The appearance of neutralizing antibodies seems to be related to a reduction of interferon β efficacy in some patients who used the drug. See William Sibley et al., Letter to the Editor, *Anticytokine Antibodies in Beta-Interferon-Treated Patients*, 50 NEUROLOGY 1930 (1998). Recent studies show that the therapeutic effectiveness of interferon β -1b is diminished in patients with multiple sclerosis who develop neutralizing antibodies to the drug. See The IFNB Multiple Sclerosis Study Group and the University of British Columbia MS/MRI Analysis Group, *Neutralizing Antibodies During Treatment of Multiple Sclerosis with Interferon Beta-1b: Experience During the First Three Years*, 47 NEUROLOGY 889, 889 (1996). However, the multicenter team that studied the effects of neutralizing antibodies in these MS patients reported that treatment with interferon β -1b still provides a “meaningful” benefit to MS patients despite the immune reaction. See *id.* at 894. If antibodies are directed against Betaseron, those antibodies are likely directed to the protein portion of Avonex as well. See *Phase IV Studies Will Evaluate Avonex Use Beyond Two Years*, PINK SHEET, May 27, 1996, at 13, 13. The FDA committee that approved Avonex noted that the clinical trial data does not address the potentially limiting effects of interferon β -neutralizing antibodies, among other factors, in Avonex treatment lasting more than two years. See *Biogen Avonex Reduces Disability Progression in MS Patients, FDA Advisory Committee Finds; Duration of Avonex Treatment Effect Requires Further Study*, PINK SHEET, Dec. 11, 1995, at 5, 5–6 (1995). One committee member said: “Your data show that the blocking antibodies don’t show up until largely year two. Given your primary endpoint of requiring a six-month sustained exacerbation, I think it’s just simply unanswered whether the occurrence of these blocking antibodies over time will make a difference.” *Id.*

182. See *Berlex Lab., Inc. v. FDA*, 942 F. Supp. 19, 22 (D.D.C. 1996).

183. See *Berlex Lab.*, 942 F. Supp. at 22.

184. See *Interferon-beta-1a Approved*, *supra* note 174, at 5.

sclerosis patients.¹⁸⁵ In that trial, patients receiving a weekly injection of interferon β -1a into their muscles (not subcutaneously) had a 37% reduction in the risk of clinically significant disability progression within the period of the study, compared with patients who received placebo.¹⁸⁶ Furthermore, 32% of placebo-treated patients had three or more exacerbations over the course of two years, compared with only 14% of interferon β -1a-treated patients.¹⁸⁷ Patients in the interferon β -1a group also had a statistically significant reduction in active brain lesions seen on magnetic resonance imaging scans.¹⁸⁸ The overall Avonex treatment was well-tolerated. Only 9% of the patients receiving the drug stopped treatment, half of them due to side effects (flu-like symptoms, muscle aches, fever, chills, and asthenia).¹⁸⁹ Injection-site reactions associated with interferon β -1a treatment occurred in only 4% of patients, not significantly different from patients in the placebo group.¹⁹⁰ There were no reports of tissue death at the injection site, possibly because of the much lower dose, the much less frequent injections, and the intramuscular, rather than subcutaneous, injection route.

The FDA's decision was based on its Orphan Drug Act regulations providing that a new drug will not be considered the same as the previously approved drug if the new drug is "clinically superior."¹⁹¹ The

185. See Jacobs et al., *supra* note 175, at 285–94.

186. See *id.* at 288. The primary endpoint was time to progression of disability, defined as an increase in the Kurtze Expanded Disability Status Scale (EDSS) of 1.0 point more than that on entry and persisting for at least six months. Secondary endpoints included the frequency of exacerbations and proportion of patients who were exacerbation-free at two years, as well as studies of magnetic resonance imaging data and side effects. The EDSS is the standard tool used in clinical trials for evaluating disability progression in multiple sclerosis. The Kaplan-Meier estimate of the proportion of patients progressing by the end of 104 weeks was 34.9% in the placebo group and 21.9% in the interferon β -1a-treated group. At the end of one year of treatment, 20.1% of placebo-treated patients had progressed by 1.0 EDSS units, compared to 12% of patients on recombinant interferon β -1a. At two years, 36.3% of placebo patients had progressed, compared to 22.6% of treated patients. See *id.*

187. See *id.* at 289. Interferon β -1a treated patients had significantly less frequent exacerbations, compared to the placebo group. Patients receiving recombinant interferon β -1a had approximately one-third fewer exacerbations (0.61 disease flare-ups per year) than patients receiving placebo (0.9 exacerbations per year). This is a 31% reduction in relapse rate among treated patients. Placebo patients were twice as likely to have three or more attacks during the study as were treated patients. See *id.*

188. See *id.* at 289–90.

189. See *id.* at 291; *Interferon-beta-1a Approved*, *supra* note 174, at 5.

190. See *Interferon-beta-1a Approved*, *supra* note 174, at 5.

191. See 21 C.F.R. § 316.3(b)(13)(ii) (1999).

Same drug means . . . [i]f it is a drug composed of large molecules (macromolecules), contains the same principal molecular structural

regulations provide further that a new drug is “clinically superior” if it offers “greater safety in a substantial portion of the target populations.”¹⁹² Based upon the results of the clinical trials, the FDA concluded that Avonex was “‘clinically superior’ to Betaseron and therefore ‘different’ for Orphan Drug Act purposes.”¹⁹³ The FDA decision decided that Avonex was safer than Betaseron, basing its conclusion on the substantially less frequent occurrence of the death of skin tissue in the injection area (injection site necrosis) associated with Avonex (0%) compared with Betaseron (5%).¹⁹⁴ The FDA also noted that 4% of Avonex patients experienced injection site reactions, compared to 85% of Betaseron patients.¹⁹⁵ The FDA’s decision was apparently based solely on the clinical data in support of the two manufacturers’ applications. The FDA neither attempted to determine whether the difference in the adverse effects of the two drugs was due to the dosing and administration differences or the actual biochemical properties of the two drugs, nor whether Avonex was more effective than Betaseron in treating the underlying disease.¹⁹⁶

features (but not necessarily all of the same structural features) and is intended for the same use as a previously approved drug, except that, if the subsequent drug can be shown to be clinically superior, it will not be considered to be the same drug. This criterion will be applied as follows to different kinds of macromolecules:

- (A) Two protein drugs would be considered the same if the only differences in structure between them were due to post-translational events or infidelity of translation or transcription or were minor differences in amino acid sequence; other potentially important differences, such as different glycosylation patterns or different tertiary structures, would not cause the drugs to be considered different unless the differences were shown to be clinically superior.

Id.

192. *See id.* at § 316.3(b)(3)(ii).

193. *Berlex Lab., Inc. v. FDA*, 942 F. Supp. 19, 22 (D.D.C. 1996).

194. *See id.* at 23.

195. *See id.* at 22.

196. Under the FDA’s Orphan Drug Regulations, *see Proposed Regulation, supra* note 9, a determination of clinical superiority based on superior efficacy generally would require that the second drug testing measure the same clinically relevant end-points as the first drug testing and at the same time intervals. Avonex’s trial was sufficiently different in design from Betaseron’s that the efficacy data for the two drugs cannot be directly compared. In what might be considered an ironic sequel to the Avonex-Betaseron controversy, the FDA denied Orphan Drug approval to Serono, a third applicant for inteferon β , on March 1, 1999. Serono had argued that its clinical trials demonstrated its inteferon β -1a drug, known as Rebif, to be superior to Avonex in three ways:

While Avonex must be mixed with a sterile solution before it is

VI. COMPARING PATENT LAW AND THE ORPHAN DRUG ACT

A. Incentives for Research and Development

The use of market exclusivity as an incentive for investment in R&D hardly originated with the Orphan Drug Act. The fundamental purpose of patent law, going back to the United States Constitution, has been to encourage R&D or, in the language of the Constitution, "progress."¹⁹⁷ Of course, if progress is the ultimate purpose, then the question which inevitably and repeatedly arises is whether a particular second claimant's work is sufficiently different from a prior claimant's work as to merit the appellation "progress" or, alternatively, is so similar as to constitute an infringement of the prior claimant's exclusive rights. Thus, this question of same versus different, which is dealt with in the Orphan Drug Act and *Berlex Laboratories*, is a very well-studied problem for patent law¹⁹⁸ and generally serves the same purposes in patent law as in the Orphan Drug Act.

In patent law, the legal definition of sameness adjusts the economic risk between the innovator and the second-comer.¹⁹⁹ Companies use the standards of protection developed in patent law to guide their investments in R&D.²⁰⁰ Because pharmaceutical companies can

injected into the muscle, Rebif comes premixed in syringes for injections beneath the skin. More importantly, Serono said Rebif comes in several doses, while Avonex is only approved for one dose. Serono executives have argued that stronger doses of beta interferon work better for patients with more advanced multiple sclerosis. Its research, however, did not include head-to-head trials comparing Avonex and Rebif.

Alex Pham, *US Rejects Serono Bid to Sell Drug: FDA Says Biogen's Avonex Maintains Rights Under Orphan Act*, BOSTON GLOBE, Mar. 2, 1999, at D1.

197. U.S. CONST. art. I, § 8, cl. 8 ("The Congress shall have Power . . . To promote the Progress of Science and useful Arts, by securing for limited Times to Authors and Inventors the exclusive Right to their respective Writings and Discoveries").

198. See generally *Graham v. John Deere Co.*, 383 U.S. 1 (1966).

199. See *Patlex Corp. v. Mossinghoff*, 758 F.2d 594, 599 (Fed. Cir.) ("The encouragement of investment-based risk is the fundamental purpose of the patent grant . . ."), modified, 771 F.2d 480 (Fed. Cir. 1985).

200. See *Hilton Davis Chem. Co. v. Warner-Jenkinson Co.*, 62 F.3d 1512, 1533 (Fed. Cir. 1995) (Newman, J., concurring), rev'd, 520 U.S. 17 (1997); see also Henry G. Grabowski, *The Determinants of Industrial Research and Development: A Study of the Chemical, Drug, and Petroleum Industries*, 76 J. POL. ECON. 292 (1968) (finding that fields that have high research costs tend to be more dependent on the patent system as an incentive for innovation); Suzanne Scotchmer, *Standing on the Shoulders of Giants: Cumulative Research and the Patent Law*, 5 J. ECON. PERSP. 29 (1991) (discussing whether patent protection provides incentives for cumulative research).

compare their potential product with another drug that is already approved or further along in development in light of the relevant standards of patent law, they can avoid investing in R&D of too similar a drug.²⁰¹ By the same token, companies that are considering the investment in developing a clearly new and innovative product use the patent law standards to better estimate the value of the protection likely to be afforded to their product. Some have suggested incentives are also needed for commercializing existing inventions, for “technologic growth benefits not only from the activities of the originators, but also from those who improve, enlarge, and challenge.”²⁰² This argument focuses on the additional innovation costs needed to bring an invention to the marketplace successfully. Furthermore, the disclosure and enablement of patents enrich the public’s knowledge base. From any of these perspectives, the patent system’s goals are similar to the stated goals of the Orphan Drug Act.

B. The Requirements for Innovation

The requirements for orphan drug protection differ from those of patent protection. A patentable drug must be a novel, useful, and nonobvious invention.²⁰³ Thus, the requirement of innovation is the central requirement for a patent. By contrast, an orphan drug must treat a rare disease and have a useful scientific rationale, but need not be a new or nonobvious chemical entity or even a nonobvious use of an existing chemical entity. The Orphan Drug Act’s exclusivity was, at least in part, designed to provide protection when patent protection was not available and the potential value of known compounds for the treatment of rare diseases was not worth commercial investment without some other form of market protection or incentives.²⁰⁴ For orphan drugs, the question of innovation, or novelty, and nonobviousness, is secondary and does not arise until a competitor seeks to serve the same population as an approved orphan drug. Thus, it is not surprising that the concept of same versus different has been given less attention and has been less fully developed in orphan drug law than in patent law, with the latter’s two hundred-year history of rewarding innovation.

201. See Levitt & Kelsey, *supra* note 89, at 526–27.

202. *Hilton Davis*, 62 F.3d at 1531–32 (Newman, J., concurring). See also Thomas F. Poche, Note, *The Clinical Trial Exemption from Patent Infringement: Judicial Interpretation of Section 271(e)(1)*, 74 B.U. L. REV. 903, 908 (1994).

203. See 35 U.S.C. §§ 100–103 (1994).

204. See *supra* text accompanying note 7.

The basis of patent protection is the nonobviousness of the invention when compared to that which was previously known (in patent law terms, "the prior art").²⁰⁵ In addition, when a second party produces a product that bears a close similarity to a previously patented invention, the "doctrine of equivalents"²⁰⁶ and the "reverse doctrine of equivalents"²⁰⁷ are patent law doctrines that have been judicially developed to determine whether the second, similar invention is sufficiently different to avoid infringement.²⁰⁸

C. Doctrine of Equivalents

In patent law, when the owner of a patent wishes to enforce her exclusive patent rights against a would-be competitor, she would bring an action in infringement.²⁰⁹ If the accused infringing product is clearly identical to the patentee's invention, the case would be considered one of literal infringement. Literal infringement occurs when every limitation in the claim²¹⁰ is found in the accused product or process. To avoid literal infringement, the developer of a second, competitive product might make changes in the product. Where the alleged infringer has simply made minor, easy, or relatively obvious changes in the product, the courts have developed the equitable doctrine of equivalents

205. See 35 U.S.C. § 103 (1994); see also *Graham v. John Deere Co.*, 383 U.S. 1 (1966).

206. See *Hilton Davis*, 62 F.3d at 1516–18.

207. See *Texas Instruments, Inc. v. U.S. Int'l Trade Comm'n*, 846 F.2d 1369, 1371–72 (Fed. Cir. 1988), *denying reh'g*, 805 F.2d 1558 (Fed. Cir. 1986); see also *Graver Tank & Mfg. Co. v. Linde Air Prods. Co.*, 339 U.S. 605, 608 (1950).

208. Some commentators have suggested that the FDA Orphan Drug regulations regarding "sameness" are similar to the patent law nonobviousness doctrine of 35 U.S.C. § 103. See Philippe Ducor, *New Drug Discovery Technologies and Patents*, 22 RUTGERS COMPUTER & TECH. L.J. 369, 473 (1996). Furthermore, the definition of "clinical superiority" could be seen as similar to the holding of *In re Papesch*, 315 F.2d 381, 391 (C.C.P.A. 1963), that prima facie structural obviousness may be rebutted by showing that the chemical compound has unexpected or advantageous properties. Nevertheless, despite the logical power of the analogy, the level of innovation ("difference") required to admit a second drug to orphan status may be less than the nonobviousness required for patent law purposes. See Ducor, *supra*. This may well have been the case in *Berlex Labs*.

209. See 35 U.S.C. § 271 (1994).

210. See *Jurgens v. McKasy*, 927 F.2d 1552, 1560 (Fed. Cir. 1991). A patent claim is an assertion of what the invention purports to accomplish; claims (found at the end of a patent) define the invention and the extent of the grant. Any feature of an invention not stated in the claims is beyond the scope of patent protection. See 35 U.S.C. § 112, para. 2 (1994).

to prevent “what is in essence a pirating of the patentee’s invention.”²¹¹ For example, an accused product or process may infringe a patent if it performs substantially the same function in substantially the same way to give substantially the same results, because, in patent law, “if two devices do the same work in substantially the same way, and accomplish substantially the same result, they are the same, even though they differ in name, form, or shape.”²¹²

The Federal Circuit and the Supreme Court have recently reexamined the test for infringement under the doctrine of equivalents. In *Hilton Davis Chemical Co. v. Warner-Jenkinson Co.*,²¹³ the Federal Circuit reaffirmed the validity of the doctrine and held that its touchstone is whether or not “substantial differences” exist between the accused process and the patented process.²¹⁴ The court also held that the question of equivalence is for the jury to decide.²¹⁵ The Supreme Court reversed and remanded the case, but also upheld the viability of the doctrine while ruling that the determination of equivalence should be applied as an objective inquiry on an element-by-element basis.²¹⁶ According to the Supreme Court, “the particular linguistic framework used” to determine “‘equivalence,’” “whether the so-called ‘triple identity’ test” or the “‘insubstantial differences’” test, “is less important than whether the test is probative of the essential inquiry: Does the accused product or process contain elements identical or equivalent to each claimed element of the patented invention?”²¹⁷ Thus, the major impact of the Supreme Court’s review of the doctrine of equivalents in *Hilton Davis* is in this requirement of element-by-element analysis.

In light of *Hilton Davis*, if the Orphan Drug Act were to incorporate something akin to the equitable patent doctrine of equivalents, how would it apply? What are the “claims” allowed by the FDA’s granting

211. *Loctite Corp. v. Ultraseal Ltd.*, 781 F.2d 861, 870 (Fed. Cir. 1985). See also *Hormone Research Found., Inc. v. Genentech, Inc.*, 904 F.2d 1558, 1564 (Fed. Cir. 1990).

212. *Graver Tank*, 339 U.S. at 608 (quoting *Union Paper-Bag Mach. Co. v. Murphy*, 97 U.S. 120, 125 (1877)); see also *Sanitary Refrigerator Co. v. Winters*, 280 U.S. 30, 41–42 (1929) (“There is a substantial identity, constituting infringement, where a device [copies a claimed device,] without variation[s] or with such variations ‘as are consistent with its being in substance the same thing.’” (quoting *Burr v. Duryee*, 68 U.S. (1 Wall.) 531, 573 (1863))).

213. 62 F.3d 1512 (Fed. Cir. 1995), *rev’d*, 520 U.S. 17 (1997).

214. See *id.* at 1520. “This case presents an opportunity to restate — not to revise — the test for infringement under the doctrine of equivalents.” *Id.* at 1516.

215. See *id.* at 1522.

216. See *Warner-Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17 (1997).

217. *Id.* at 39–40.

of a seven-year period of market exclusivity? It would appear most logical to consider Orphan Drug Act market exclusivity as consisting of essentially one claim: "the use of compound A in the treatment of disease X." In *Hilton Davis* terms, it would seem that the Orphan Drug Act creates a very simple, two-element claim, consisting of a compound or composition of matter element and a disease or, in FDA terms, "indication" element. Of course, the issue of market exclusivity only arises where there is in fact identity between the second applicant's indication and the first sponsor's approved orphan indication. The more difficult issue is whether, in doctrine of equivalent terms, the second sponsor's compound performs the same function in the same way or, alternatively, whether the differences between the second applicant's drug and the first approved drug are insubstantial. Before examining that question, it is necessary to explore briefly the reverse doctrine of equivalents, a second judicially-created patent doctrine which is closely bound up with the doctrine of equivalents.

D. Reverse Doctrine of Equivalents

Although the doctrine of equivalents was created to provide a patentee with equitable protection against competitors who would avoid literal infringement by making obvious or easy changes to the patentee's invention, the reverse doctrine of equivalents was judicially created for the reciprocal problem. The reverse doctrine of equivalents protects second inventors where their product might be viewed as literally infringing a prior invention, yet works in a substantially different way or produces a substantially different result.²¹⁸ In these situations, the reverse doctrine serves the same equitable purpose as the doctrine of equivalents by allowing the patented invention to be construed in such a way that the form of the claim does not triumph over the substance of the patented invention.²¹⁹

218. An accused article may avoid infringement, even if it is within the literal words of the claim, if it is "so far changed in principle from a patented article that it performs the same or a similar function in a substantially different way." *Graver Tank & Mfg. Co. v. Linde Air Prods. Co.*, 339 U.S. 605, 608-09 (1950).

219. See *Scripps Clinic & Research Found. v. Genentech, Inc.*, 927 F.2d 1565, 1561 (Fed. Cir. 1991); *Pennwalt Corp. v. Durand-Wayland, Inc.*, 833 F.2d 931, 947 (Fed. Cir. 1987); *In re Hogan*, 559 F.2d 595, 607 (C.C.P.A. 1977) ("Like the judicially-developed doctrine of equivalents, designed to protect the patentee with respect to later-developed variations of the claimed invention, the judicially-developed 'reverse doctrine of equivalents,' requiring interpretation of claims in light of the specification, may be safely relied upon to preclude improper enforcement against later developers.").

The purpose of the “reverse” doctrine is to prevent unwarranted extension of the claims beyond a fair construction of the first inventor’s contribution.²²⁰ The contribution of an inventor is used here to refer to that which the inventor’s patent application has truly enabled others to do.²²¹ A patentee must provide a sufficient description of her invention to enable others to practice the invention and is not entitled to a patent that claims more than what is enabled. Thus, the reverse doctrine of equivalents protects a second innovator who can truly assert that her claimed invention was not made possible (i.e., enabled) by what was described by the prior inventor, and bars enforcement in such cases against later true innovators.²²²

E. Unexpected Results

One additional concept of patent law that is closely related to the reverse doctrine of equivalents and to the Orphan Drug Act’s “same versus different” problem is the rule that a second compound will be patentable (in particular with respect to nonobviousness), despite its structural similarity to a prior compound, if the second applicant can provide evidence of unexpected results produced by the second compound.²²³ Under this rule, once the Patent and Trademark Office demonstrates a structural similarity between the prior art and the second compound and that the prior art would suggest a reason to make the second compound, it has established the *prima facie* obviousness of the second compound.²²⁴ The burden then shifts to the applicant to rebut, in some cases by “a comparison of test data showing that the claimed compositions possess unexpectedly improved properties . . . that the prior art does not have”²²⁵ In such cases, the evidence of unexpected results can be thought of as a close sibling of the doctrine of reverse equivalents, for the unexpected results are a firm basis for arguing that the second compound, despite its similarity to the first, performs its function in a substantially different way. The doctrine of reverse equivalents is used where the second compound is accused of infringing, while the evidence of unexpected results is used when the

220. See *Scripps Clinic*, 927 F.2d at 1561.

221. See generally 35 U.S.C. § 112, para. 1; Edward T. Lentz, *Adequacy of Disclosures of Biotechnology Inventions*, 16 AM. INTELL. PROP. L. ASS’N Q.J. 314 (1989).

222. See *Hogan*, 559 F.2d at 607.

223. See *In re Mayne*, 104 F.3d 1339, 1342 (Fed. Cir. 1997).

224. See *id.*

225. *Id.* (citations omitted).

second compound is denied a patent on the grounds that a prior compound rendered it obvious.

How do these three areas of patent law relate to the Orphan Drug Act problem faced by the FDA? It would seem that when the FDA finds that a second, similar drug is the same as a prior orphan drug, it is essentially making the determination that a court would make in deciding that a second, similar item infringes a prior invention under the doctrine of equivalents. Similarly, when the FDA makes a finding that a second, similar drug is different from a prior orphan drug because it is clinically superior to the first, it is very much like a court determining that a second is not infringing under the doctrine of reverse equivalents or acting as a court does in determining that a second compound is independently patentable because it provides unexpected results.

In patent law, the two verbal formulations discussed in the Supreme Court's opinion in *Hilton Davis*²²⁶ have been developed over the course of a century of patent law to deal with all technologies, from metallurgy to biotechnology to aerospace engineering, while the evidence of unexpected results developed over the past thirty years to deal primarily with chemical compounds.²²⁷ The FDA is at a considerable advantage in formulating its Orphan Drug Act approach to the problem of sameness because its approach need only fit a relatively confined problem, namely the identity of two structurally similar drugs. It is a problem that the

226. See *Warner-Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 39–40 (1997).

Both the parties and the Federal Circuit spend considerable time arguing whether the so-called 'triple identity' test — focusing on the *function* served by a particular claim element, the *way* that element serves that function, and the *result* thus obtained by that element — is a suitable method for determining equivalence, or whether an "insubstantial differences" approach is better. There seems to be substantial agreement that, while the triple identity test may be suitable for analyzing mechanical devices, it often provides a poor framework for analyzing other products or processes. On the other hand, the insubstantial differences test offers little additional guidance as to what might render any given difference "insubstantial."

In our view, the particular linguistic framework used is less important than whether the test is probative of the essential inquiry: Does the accused product or process contain elements identical or equivalent to each claimed element of the patented invention? Different linguistic frameworks may be more suitable to different cases, depending on their particular facts.

Id. at 39–40.

227. See, e.g., *Mayne*, 104 F.3d 1339.

FDA must deal with in contexts outside the Orphan Drug Act, and one for which greater precision than is provided by the FDA's Orphan Drug Act regulations is clearly attainable. Despite the obvious similarity between the FDA's concept of clinical superiority and the patent law's evidence of unexpected results, the FDA can and should do much more to clarify the clinical superiority standard and procedures. Much of what the FDA needs to do has, in fact, already been done by it in other contexts.

VII. HOW THE FDA DETERMINES SAME AND DIFFERENT FOR DRUGS IN OTHER CONTEXTS

A. *The FDA Guidance Document Concerning Demonstration of Comparability of Human Biological Products*

Just weeks before the FDA approved Avonex, it published a Guidance Document regarding changes in the manufacturing processes of "well-characterized" biological drugs.²²⁸ The FDA issued this Guidance Document to provide pharmaceutical manufacturers with greater flexibility in bringing biological products to market efficiently and expeditiously.²²⁹ Until that time, companies developing biotechnology drugs such as recombinant proteins or monoclonal antibodies faced a considerably more complicated regulatory pathway through CBER (the FDA's Center for Biologics Evaluation and Research) than did companies developing small molecules through CDER (the FDA's Center for Drug Evaluation and Research) because

228. See GUIDANCE DOCUMENT, *supra* note 12.

229. See *id.* at 1.

FDA is issuing this guidance document as part of its on-going initiatives to provide manufacturers with increased flexibility to bring important and improved human biological products to market more efficiently and expeditiously. This document addresses the concept of product comparability and describes current FDA practice concerning product comparability of human biological products regulated by the Center for Biologics Evaluation and Research (CBER), including therapeutic biotechnology-derived products, regulated by CBER, and therapeutic biotechnology-derived products regulated by the Center for Drug Evaluation and Research (CDER). 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.

Id.

approval of a biologic required two separate applications and approvals: (1) the approval of the product as safe and effective, through the submission of a product license application ("PLA"); and (2) the submission of an establishment license application ("ELA") for approval of the manufacturing facility that produced the actual material used to generate the data in the PLA.²³⁰ The rationale for the two-part, inter-related approval process for biologics was that the manufacture of biological molecules was such a highly variable process that a change from one facility to another could produce a change in the product itself. In addition, the manufacturer was required to verify the product's identity for each lot produced.²³¹ The FDA had traditionally refused to approve applications unless clinical trials were conducted with the specific product to be licensed because "[a]ny change in the product during the clinical trial could be problematic because clinical data obtained with variants of the product described in the PLA might *not* be acceptable to support licensure of that PLA."²³²

The Guidance Document is part of a greater policy to harmonize the requirements across the FDA for pharmaceutical manufacturers to produce "well-characterized" biotechnology drugs.²³³ The policy of increased flexibility is possible because recent advances in "techniques for isolation of macromolecules, product and process related," and "ability to establish sensitive and validated assays for characterizing the product and biological activity"²³⁴ have provided the scientific ability to control the manufacture of biotechnology drugs. The FDA has found that it can review most biotechnology drugs without requiring a separate

230. See JAMES T. O'REILLY, FOOD AND DRUG ADMINISTRATION § 13.22 (2d ed. 1995).

231. See *id.*

232. CENTER FOR BIOLOGICS EVALUATION AND RESEARCH, POINTS TO CONSIDER IN THE MANUFACTURE AND CLINICAL EVALUATION OF IN VITRO TESTS TO DETECT ANTIBODIES TO THE HUMAN IMMUNODEFICIENCY VIRUS, TYPE 1 (1989), available at <<http://www.fda.gov/cber/points.htm>>. See also Changes to an Approved Application, 61 Fed. Reg. 2739 (1996) (to be codified in scattered sections of 21 C.F.R.) (proposed Jan. 29, 1996).

233. See CLINTON & GORE, *supra* note 45.

234. GUIDANCE DOCUMENT, *supra* note 12, at 4. Among the recently developed tests regarding identity, purity, stability and consistency are amino acid analysis, amino acid sequencing, peptide mapping, determination of disulfide linkage, Sodium Dodecyl Sulfate-Polyacrylamide Gel Electrophoresis (SDS-PAGE), isoelectric focusing, High Pressure Liquid Chromatography (HPLC), mass spectroscopy, assays to detect product-related proteins including deamidated, oxidized, cleaved, and aggregated forms and other variants, assays to detect residual host proteins, DNA, and reagents, immunochemical analyses, and assays to quantitate bioburden. All of these tests can be or have been done for both interferon β -1a and interferon β -1b.

regulation and licensure of the product and the establishment, or manufacturing facility.²³⁵ The new procedures replace the separate PLA and ELA with a single application, the Biologics License Application (“BLA”).²³⁶ Central to the new BLA procedure is the FDA’s confidence that it can provide clear guidelines to manufacturers that will enable them to show that the protein produced in one facility and that was used in clinical trials is the same as the protein produced in another facility, which is the purpose of the Guidance Document.

The Guidance Document states that FDA regulations allow it to approve biological products based on clinical data from a “precursor product” if it is comparable to the product seeking approval. Because of improvements in production methods and test methods for biotechnology product characterization, the pharmaceutical manufacturer may not need to perform additional clinical studies to demonstrate safety, purity, and potency when the manufacturer changes its manufacturing process before FDA drug approval of its product, but after completion of a pivotal clinical study.²³⁷ The FDA now interprets the phrase, “data derived from nonclinical laboratory and clinical studies which demonstrate that the manufactured product meets prescribed standards of safety, purity, and potency”²³⁸ to include clinical data generated from a precursor product, so that the FDA may not require conducting additional clinical trials to demonstrate efficacy.²³⁹

In allowing the clinical data for a “precursor” product to be used for a later product, the FDA is now willing to examine the results of “analytical testing, biological assays (in vitro or in vivo), assessment of pharmacokinetics and/or pharmacodynamics and toxicity in animals,”²⁴⁰ as well as clinical testing, to determine whether or not the later product is the same as a prior composition. In other words, the FDA now feels that the science of genetic engineering of proteins has advanced to the point where a variety of tests can determine whether a change in manufacturing a protein yields the same protein or a different one for product identity purposes. Ironically, although the FDA relied on such principles to determine that Avonex could use clinical data generated by a prior compound,²⁴¹ it ignored them completely in making its Orphan

235. See CLINTON & GORE, *supra* note 45.

236. See 63 Fed. Reg. 3145 (1998).

237. See GUIDANCE DOCUMENT, *supra* note 12.

238. 21 C.F.R. § 601.2(a) (1999).

239. See GUIDANCE DOCUMENT, *supra* note 12.

240. *Id.* at 5.

241. See *Berlex Lab., Inc. v. FDA*, 942 F. Supp. 19, 23 (D.D.C. 1996).

Drug Act determination that Avonex and Betaseron were different drugs based its finding of clinical superiority.

When it proposed the Orphan Drug regulations, the FDA was concerned about determinations that involved too much judgment and discretion on the part of FDA officials.²⁴² Then, the FDA rejected any approach where the kinds of structural differences likely to be related to differences in pharmacological activity were not specified.²⁴³ With the Guidance Document now in place, FDA officials appear to have more of the tools required to make judgments about the kinds of structural differences likely to be related to differences in pharmacological activity when determining the similarity of well-characterized biological drugs. FDA officials also have the discretion to decide whether further clinical trials are required. The Guidance Document provides a major science policy basis for a further clarification of the Orphan Drug Act's same versus different problem.

B. The FDA's Regulations for the Approval of Generic Drugs

The FDA has had a great deal of experience in determining when two drugs are identical, because that function is required during the approval of generic versions of drugs for which patent protection is expiring. When a company's patent monopoly expires, the company does not stop manufacturing the drug, even though competitors can market the medication in a generic form, which will likely cost less than the branded form previously available from the patent holder.²⁴⁴ In 1988, generic drug market share averaged thirty percent in the first year after patent expiration. More recently, Syntex's arthritis drugs lost two-thirds of the market to generics within one month of patent expiration.²⁴⁵

The process of generic drug approval is much simpler and less costly than the approval of new drugs. A manufacturer of an orphan drug that is also protected by patent exclusivity is unlikely to open itself to generic competition by seeking approval for a non-orphan indication. Instead, the manufacturer can build off-label usage for its orphan drug

242. See Proposed Regulations, *supra* note 9, at 3341.

243. See *id.*

244. See Elyse Tanouye, *Price Wars, Patent Expirations Promise Drugs*, WALL ST. J., Mar. 24, 1994, at B1; see also Lance W. Rook, *Listening to Zantac: The Role of Non-prescription Drugs in Health Care Reform and the Federal Tax System*, 62 TENN. L. REV. 107, 116 (1994).

245. See Tanouye, *supra* note 244; see also Jonathan C. Peck, *The Long-Term Effects of Recent Legislation on the Drug Industry*, 43 FOOD DRUG COSM. L.J. 541, 542-43 (1988); Rook, *supra* note 244, at 116.

by distributing journal articles that support the additional uses. If the non-orphan indication were instead added to the label, a generic competitor could quickly gain approval by submitting bioavailability²⁴⁶ and bioequivalence²⁴⁷ studies.²⁴⁸

A generic version of a drug is chemically identical to the original pioneer drug and, therefore, can rely on the safety and efficacy studies done for the pioneer drug. Abbreviated applications for approval can be filed for generic versions of drug products that have been previously approved under a full new drug approval.²⁴⁹ All that is required are bioavailability and bioequivalence studies,²⁵⁰ which are relatively simple

246. See 21 C.F.R. § 320.1(a) (1999) ("Bioavailability means the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action.").

247. See *id.* § 320.1(e) ("Bioequivalence means the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.").

248. See Rin-Laures & Janofsky, *supra* note 39, at 281–82.

249. See 21 C.F.R. § 314.54.

250. See 21 C.F.R. § 320.24 (Types of evidence to establish bioavailability or bioequivalence).

(a) Bioavailability or bioequivalence may be determined by several in vivo and in vitro methods. FDA may require in vivo or in vitro testing, or both, to establish the bioavailability of a drug product or the bioequivalence of specific drug products. . . .

Applicants shall conduct bioavailability and bioequivalence testing using the most accurate, sensitive, and reproducible approach available among those set forth in paragraph (b) of this section. . . .

(b) The following in vivo and in vitro approaches, in descending order of accuracy, sensitivity, and reproducibility, are acceptable for determining the bioavailability or bioequivalence of a drug product.

(1)(i) An in vivo test in humans in which the concentration of the active ingredient or active moiety, and, when appropriate, its active metabolite(s), in whole blood, plasma, serum, or other appropriate biological fluid is measured as a function of time. This approach is particularly applicable to dosage forms intended to deliver the active moiety to the bloodstream for systemic distribution within the body; or

(ii) An in vitro test that has been correlated with and is predictive of human in vivo bioavailability data; or

(iii) An in vivo test in animals that has been correlated with and is predictive of human bioavailability data.

and much less expensive than the detailed pre-clinical and clinical investigations required for a full New Drug Application.²⁵¹

The tests for bioavailability and bioequivalence measure important aspects of the pharmacokinetics of a drug.²⁵² If two drugs that are very similar in structure have nearly identical pharmacokinetics, one would presume that whatever differences in structure exist would not be pharmacologically important or clinically relevant. That is because such important pharmacologically or clinically relevant differences — e.g., in the two drugs' affinity for their target molecule (ligand) or their relative antigenicity — would be expected to cause marked differences in pharmacokinetics for most, if not all drugs.²⁵³

VIII. CONCLUSION: BIOEQUIVALENCE CREATES A PRESUMPTION THAT SIMILAR DRUGS ARE THE SAME UNDER THE ORPHAN DRUG ACT

In patent law, the inquiry as to whether a second item that is more or less closely related to an earlier invention, is entitled to its own protection, or infringes the earlier patentee's rights, takes place under the doctrine of equivalence, the doctrine of reverse equivalents, and the evidence of unexpected results. Each of these doctrines addresses a common, core concern: Does the second item make a substantial and independent contribution, or is it merely an attempt to profit from the exploitation of the earlier inventor's contribution? The Orphan Drug Act, enacted in 1983, created an analogous problem in prohibiting the FDA from approving "another license . . . for such drug for such disease or condition . . . until the expiration of seven years"²⁵⁴ The obviously analogous problem for the administration of the Orphan Drug Act is determining when a second, similar drug is the same as "such drug" and therefore barred from FDA approval, and when a second,

251. See 21 C.F.R. §§ 320.21–.31.

252. "Pharmacokinetics refers to the way our body handles drugs (absorption, distribution, metabolism, and excretion). So pharmacokinetics relates to the disposition or movement of drugs in the body." University of Florida, College of Medicine, Office of Medical Informatics, *Geriatric Education Cases, Glossary* (last modified Apr. 13, 1999) <<http://www.medinfo.ufl.edu/cme/geri/glossary.html>>.

253. See Interview with Dr. John O'Brien, Professor of Medicine, University of California at San Diego, in San Diego (Mar. 26, 1998). In those cases where similar pharmacokinetics masked a biologically and clinically relevant difference between similar drugs, the effect of the proposal here would be to impose on the second applicant the additional burden of demonstrating that clinical difference in a head-to-head comparison.

254. 21 U.S.C. § 360cc (1994 & Supp. III 1997).

similar drug is sufficiently different to be entitled to its own market exclusivity.

Soon after the enactment of the Orphan Drug Act, in the absence of any administrative interpretation of the scope of the “such drug” protection, the courts applied a much narrower interpretation to the Orphan Drug Act protection than would have been the case under patent law.²⁵⁵ The damage that such narrow readings of the Orphan Drug Act would do to the incentives of the Act were obvious, and the FDA ultimately responded with regulations that defined the scope of Orphan Drug Act exclusivity in a way that is much closer to the way that patent law resolves the issue. When the FDA concluded that the ultimate basis for determining whether a second, similar drug could be approved would rest on its demonstration of clinical superiority over the prior drug, the agency was apparently searching for a test that essentially measured whether the second applicant made a substantial and independent contribution to the treatment of the orphan disease, or whether it simply sought to profit from the same work as the first applicant.

The FDA’s reliance on clinical superiority serves two purposes. First, it furthers the interests of patients in receiving the benefits of any significant advance in therapy. Second, FDA reliance on clinical superiority serves a purpose much like that of the evidence of unexpected results or the reverse doctrine of equivalents in patent law: clinical superiority is intended by the FDA to be sufficient evidence to support a determination that the difference between the two drugs is in fact significant.

Unfortunately, *Berlex Labs* reveals the shortcomings in the FDA’s attempt to solve the same versus different drug problem by looking to clinical superiority. If clinical superiority can be demonstrated by the frequency of adverse effects where direct, head-to-head comparisons are not possible, it is difficult to know whether the second drug’s “superiority” is due to the substantial independent contribution of the second applicant or the advantage of learning from the first applicant’s data. At the same time, the FDA has clearly indicated that it would not favor a policy which required head-to-head comparisons for all structurally similar second drugs. What remains is the question of when head-to-head comparisons are most necessary and whether the cases in which head-to-head comparisons should be required can be sufficiently clarified by further guidelines.

255. See *Genentech, Inc. v. Bowen*, 676 F. Supp. 301, 313 (D.D.C. 1987) (holding that a single amino acid change in the human growth hormone protein, with no functional significance, rendered the second protein outside the licensing bar of the Orphan Drug Act).

The position taken here is that if two drugs are structurally similar and pharmacokinetically equivalent, then the FDA should presume that the second drug is the same as the first drug for Orphan Drug Act exclusivity purposes unless the second drug is shown clinically superior on the basis of clinical trials that permit a direct, head-to-head comparison. This would mean that a sponsor of an orphan drug application for a biological molecule which has substantial structural similarity²⁵⁶ to an already approved biological molecule would need to perform comparative bioequivalence and bioavailability studies for its drug and the already approved orphan drug. If those studies show substantial equivalence, then the sponsor would either have to forsake further clinical development or perform a clinical study which would give the FDA a direct, head-to-head comparative basis on which to make its determination as to whether or not the second drug is clinically superior to the first.

This suggested approach would avoid the problem of requiring costly comparative clinical studies of safety or efficacy in any case in

256. Structural similarity for most proteins would continue to be based on a comparison of linear amino acid sequences and the nature of any substitutions. However, for monoclonal antibodies, a somewhat different approach would seem appropriate. Monoclonal antibodies are proteins that are produced by specialized immune system cells and which recognize and bind to particular foreign substances, such as a surface feature of a virus or a particular protein involved in a disease process. See JAMES D. WATSON & MICHAEL GILMAN, RECOMBINANT DNA 460–63 (1996). Although no monoclonal antibodies have yet been approved as Orphan Drugs, monoclonal antibodies have been approved as therapeutics, e.g., Centocor's ReoPro, see Centocor, Inc., *Pharmaceuticals Division & Products* (visited Mar. 29, 1999) <<http://www.centocor.com/pharmdiv.htm>>, and IDEC Pharmaceutical's Rituximab, see *Rituximab for Refractory Non-Hodgkin's Lymphoma*, MED. SCI. BULL., Dec. 1997, available at <<http://pharminfo.com/pubs/msb/ritux243.html>>. It would seem that the major inventive effort in the development of a particular antibody type (e.g., Human Ig-G, or Murine Ig-M) as a therapeutic for a particular disease would be in identifying an appropriate target antigen and demonstrating its efficacy. For example, IDEC Pharmaceuticals demonstrated the viability of treating non-Hodgkins lymphoma with a humanized Ig-G antibody directed at CD20, a particular protein found on the surface of 90% of all pre-B and mature B lymphocytes (which are the cells proliferating inappropriately in non-Hodgkin's lymphoma), but is not found on stem cells, pro-B cells, normal plasma cells, or other normal tissue. See WATSON & GILMAN, *supra*, at 460–63. If such a drug were approved as an orphan drug, then the position taken here is that any Ig-G antibody, directed at the same CD20 protein for the treatment of the same disease, would have to show pharmacokinetic differences (as would be found in any case in which the antibodies differed significantly in species of origin or Ig class) or be required to undergo head-to-head comparator trials. Thus, substantial homology for monoclonal antibodies ought to be defined by the use of a particular class of antibody targeting a particular antigen for a particular disease.

which much less expensive and quicker studies of the two drugs' pharmacokinetics indicated that the drugs were non-bioequivalent. In addition, the results of the bioavailability and bioequivalence studies would create only a presumption of sameness that could be rebutted either by head-to-head clinical studies or by providing the FDA with independent in vitro or in vivo data demonstrating that, despite overall pharmacokinetic similarity, there is a scientific basis for suggesting that the difference in the two drugs would nonetheless be significant. For example, if antigenicity is expected to develop only after repeated doses over a long period of time, then a slight structural change that affects long-term antigenicity would not be expected to be reflected in standard assays of bioequivalence or other pharmacokinetic studies. In such cases the sponsor might draw on other principles of comparability or non-comparability to provide data supporting an FDA determination to allow the second drug to proceed without direct head-to-head comparative trials.

The proposal that the FDA modify its regulations for the Orphan Drug Act to require sponsors of similar biological drugs for the same orphan indication to include comparative data on bioequivalence would provide subsequent sponsors with a clear means of predicting whether or not their molecule would be judged to be the same as an already approved molecule. It would also serve to answer the related question of whether head-to-head clinical trials would be necessary. Furthermore, such data should be available quite early in the development process, certainly not later than Phase I of clinical testing. In many cases, animal pharmacokinetics may well provide a strong suggestion of the ultimate answer in the early, pre-clinical stage. By removing a major portion of the uncertainty which now clouds the issue of when two orphan drugs will be judged to be the same, such a relatively simple addition to the regulations may well strengthen the incentives of the Orphan Drug Act for the development of needed therapies for small patient populations.