

RECENT DEVELOPMENTS CONCERNING THE ORPHAN DRUG ACT

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INTRODUCTION

Many citizens of the United States grapple with illness every day. Some illnesses, like asthma, have a relatively high patient population. Other illnesses, like Tourette's Syndrome, a neurological disorder, are rare. Pharmaceutical companies invest substantial amounts into the research and development of treatments for the more prevalent diseases because of the high expected return. Since, by definition, "rare" diseases have small patient populations, companies have been less willing to develop drugs for these diseases. Currently, there are ten to twenty million Americans¹ suffering from more than 5,000 rare diseases.²

Before 1983, pharmaceutical companies were inclined to pass over the opportunity to investigate and market treatments for rare diseases since the costs of research and development often exceed the potential commercial market. In many cases, diseases had known potential treatments, but companies did not want to invest the time and money necessary to have a potential treatment approved by the Food and Drug Administration ("FDA") with no assurance that the costs would be recouped by sales. These potential treatments, aptly called "orphan drugs," were generally unavailable for the victims of these rare conditions.³

The Orphan Drug Act⁴ (the "Act") stemmed from a desire to encourage the development of drugs for the treatment of rare diseases.

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1. 136 CONG. REC. H11,931 (daily ed. Oct. 23, 1990) (statement of Rep. Bliley).

2. 134 CONG. REC. S3686 (daily ed. Mar. 31, 1988) (statement of Sen. Metzenbaum). Congress initially defined rare disease as a "disease or condition which occurs so infrequently in the United States that 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 . . ." 50 Fed. Reg. 19,583 (1985). Currently, Congress defines "rare disease" as a disease which affects a patient population of 200,000 or less, or a disease for which "there is no reasonable expectation" that prospective sales of the treatment in the United States will cover costs. 21 U.S.C. § 360bb(a)(2)(B) (1988).

3. Examples of diseases and conditions considered "rare" by Congress include Tourette's Syndrome, Huntington's Disease, Amyotrophic Lateral Sclerosis (Lou Gehrig's Disease), and Muscular Dystrophy. H.R. REP. NO. 840(I), 97th Cong., 1st Sess. (1982), reprinted in 1982 U.S. CODE CONG. & ADMIN. NEWS 3577, 3577.

4. Pub. L. No. 97-414, 96 Stat. 2049 (1983) (codified as amended at 21 U.S.C. §§ 360aa-360ee (1988)).

As passed by both Houses of Congress in 1983, the Act provided pharmaceutical companies with special economic incentives, making orphan drugs more attractive to develop.⁵

There is little dispute that the Orphan Drug Act has been successful.⁶ In the twenty years before it was enacted, only ten orphan drugs were approved. In the seven years since, 45 orphan drugs have been approved and another 133 are undergoing clinical trials or are awaiting review.⁷ However, there has been some debate about whether the Act is functioning as it was intended, whether it protects some drugs that do not need protection, and whether it is making orphan drugs readily available to all those who need them.

This Recent Development examines the controversies surrounding the Act in light of two events: the passage and veto of amendments to the Act last fall, and the FDA's proposed regulations to implement the Act, published earlier this year. As background, Section I explains the general drug approval process, and Section II, the history of the original Act and its subsequent amendments in 1984, 1985, and 1988. Section III describes the current incentives that are available under the Act, and the FDA's proposed regulations for implementing the Act. Section IV details abuses of the Act's market exclusivity incentive that can occur when companies attempt to gain market exclusivity protection for highly profitable drugs, and analyzes the various amendments and regulations that have been proposed to rectify these abuses. Section V discusses the impact of the proposed regulations on the scope of market exclusivity protection. Section VI outlines some of the remaining barriers to orphan

5. *See id.*

The legislation accomplishes this goal by clarifying that approval process for orphan drugs; by providing a tax credit equal to 90 percent of the cost of conducting human clinical trials as an incentive to develop orphan drugs; by offering exclusive marketing rights on unpatentable orphan drugs for a period of seven years; and by establishing an "Orphan Products Board" to coordinate the activities of federal agencies involved in drug research and regulations.

H.R. REP. NO. 840(1), *supra* note 3, at 3577.

6. It is so successful that people in foreign countries want to emulate it. For example, the Japan Pharmaceutical Manufacturers' Association has asked the Japanese Ministry of Health and Welfare to provide similar inducements for orphan drugs in that country. *Orphan-drug Inducements Sought*, *Biotechnology Newswatch*, Jan. 7, 1991, at 13.

7. 136 CONG. REC. H11,931 (daily ed. Oct. 23, 1990) (statement of Rep. Bliley). The large number of orphan drugs that have been designated and approved for marketing since 1983 are testimony to the Act's success. The Act has more than doubled the number of drugs available for rare diseases. In 1983, there were only 34 orphan drugs being marketed. H.R. REP. NO. 473, 100th Cong., 1st Sess. (1987), *reprinted in* 1988 U.S. CODE CONG. & ADMIN. NEWS 46, 47.

drug development that limit the effectiveness of the Act, and suggests several means for removing these impediments.

I. THE DRUG APPROVAL PROCESS

The road to FDA approval of any drug is long and difficult. Even before an application for drug approval is filed with the FDA, the safety and effectiveness of the drug must be shown by the drug sponsors through "adequate and controlled investigations."⁸ The clinical investigation of a drug usually occurs in three phases and follows rather rigid requirements. Phase I involves "the initial introduction of the investigational new drug into humans."⁹ It serves to establish the initial data on the drug's side effects and its relative effectiveness in patients or voluntary subjects. Phase II investigations act to "evaluate the effectiveness of the drug for a particular indication or indications in patients with the disease or condition under study."¹⁰ Phase III studies are conducted only after the effectiveness of the drug has been proven through Phase I and II clinical evaluations. The last phase is far less controlled than the previous two and is used "to gather additional information about the effectiveness and safety that is needed to evaluate the overall benefit-risk relationship of the drug and to provide an adequate basis for physician labeling."¹¹ The FDA's main concern in the regulation of these phases is to "assure the safety and rights of subjects, and . . . to help assure that the quality of the scientific evaluation of drugs is adequate to permit an evaluation of the drug's effectiveness and safety."¹² Even then, the requirements for application for an Investigational New Drug ("IND") exemption to the Food, Drug and Cosmetic Act of 1938¹³ ("FDCA") are fairly strict.

Before the FDA will authorize a drug for use in clinical investigations, the drug's sponsor must determine the pharmacological and toxicological characteristics of the drug by conducting pre-clinical tests on laboratory animals or *in vitro*.¹⁴ The term "clinical investigation" refers to "any experiment in which a drug is administered or dispensed to, or

8. 21 U.S.C. § 355(d) (1988).

9. 21 C.F.R. § 312.21 (1990).

10. *Id.*

11. *Id.*

12. *Id.*

13. Pub. L. No. 75-717, 52 Stat. 1040 (1938) (codified as amended at 21 U.S.C. §§ 360aa-360ee (1988)).

14. 21 C.F.R. § 312.23(a)(8).

used involving, one or more human subjects."¹⁵ If a sponsor wishes to conduct clinical tests with a new drug, the sponsor must submit an IND application containing the results of the pre-clinical studies and a plan for the clinical investigation.¹⁶ There can be no changes in the structure of a clinical trial without permission from the FDA, and investigational new drugs cannot be commercially marketed without IND plan approval.¹⁷ Once clinical investigations have proven the drug both safe and effective for human use, the sponsor of the drug must apply to the FDA for approval to market the drug.¹⁸ The results of the clinical investigations are submitted in the form of a New Drug Application ("NDA"). Following the approval of an NDA, the sponsor of the drug is free to market it. The entire process from IND stage to NDA stage often takes several years and several million dollars to complete, and this expenditure of time and money does not guarantee approval.¹⁹

II. THE ORPHAN DRUG ACT AND ITS AMENDMENTS

A. *The 1983 Orphan Drug Act*

The Orphan Drug Act amended the FDCA with the purpose of facilitating "the development of drugs for rare diseases or conditions."²⁰ Aiding the victims of rare diseases remains the overriding goal of the Act, although it has been amended several times since its inception. The Act in its original form created incentives to encourage the research, development, and marketing of orphan drugs. To qualify for benefits under the Act, a drug sponsor has to apply for and receive orphan designation for the drug from the FDA. The original criterion for designation was that there was "no reasonable expectation" that the costs of research

15. *Id.* § 312.3.

16. *Id.* § 312.23. This plan needs to become progressively more detailed as the phases of an investigation become more complicated. Additional requirements include the IND Safety Reports (to detail any "serious adverse experience" or "unexpected adverse experience"), *id.* § 312.32, and the Annual Report (filed within two months of the anniversary of the IND to detail the progress of the investigation), *id.* § 312.33.

17. *Id.* § 312.7. Once an IND plan is in place, the "investigational new drug . . . is exempt from the pre-marketing approval requirements that are otherwise applicable and may be shipped lawfully for the purpose of conducting clinical investigations of that drug." *Id.* § 312.1(a).

18. *Id.* § 314.2.

19. Compare the difficulty of new drug approval to the ease of generic drug approval. See *infra* note 85 (If a drug has already been approved under a full NDA, manufacturers of the generic versions need only submit abbreviated NDAs containing bioavailability data).

20. H.R. REP. NO. 840(I), *supra* note 3, at 3577.

and development of that drug would be recouped from anticipated sales of the drug within the United States.²¹

The Act provided several monetary incentives for orphan drug research and development. The first authorized the expenditure of up to four million dollars each year for grants and contracts for clinical testing of orphan treatments.²² A second incentive supplied a tax credit to orphan drug sponsors to cover fifty percent of the costs of clinical testing.²³ These two incentives were quite different from the versions in the original bills passed by the House and Senate. The House bill, sponsored by Representative Waxman, had authorized a 100% tax credit to drug sponsors and had directed a smaller amount toward clinical grants. The Senate bill had allotted more money toward clinical grants and slashed the tax credit provision. The incentives included in the final version of the Act were the result of a compromise between the two Houses. The Act also included a seven-year exclusive marketing provision which offered protection to those orphan drugs that could not be patented.²⁴ Multiple sponsors can receive designation for the same orphan drug, but only the first sponsor to receive FDA approval gains exclusive rights to market that drug. No other version of this same drug can be approved by the FDA until the seven-year period has expired. This exclusive marketing provision allows a sponsor time to recoup research and development costs.

Additionally, the Act created an Orphan Products Board under the auspices of the Department of Health and Human Services.²⁵ This provision required the Secretary of the Department of Health and Human Services to provide a drug sponsor with written recommendations on whether the sponsor's planned pre-clinical and clinical tests of an orphan drug would be adequate for approval.²⁶ Lastly, the Act authorized the wide distribution of orphan drug products, under IND approval, to those patients who need them. In the eight years since the Act was passed, the FDA has not promulgated final regulations implementing the Act. However, the FDA made interim guidelines available to pharmaceutical com-

21. See *supra* note 2.

22. Orphan Drug Act, sec. 5, 96 Stat. 2049 (1983) (codified as amended at 21 U.S.C. § 360ee (1988) (FDCA)). The Act provided for three years of such grants, to be renewed as necessary.

23. *Id.* sec. 4(a) (codified as amended at 26 U.S.C. § 28 (1988) (1954 Internal Revenue Code)).

24. *Id.* sec. 2 (codified as amended at 21 U.S.C. § 360cc (1988) (FDCA)).

25. *Id.* sec. 3 (codified as amended at 42 U.S.C. § 236 (1988) (Public Health Service Act)).

26. *Id.* sec. 2 (codified as amended at 21 U.S.C. § 360aa (1988) (FDCA)).

panies,²⁷ and has recently published proposed regulations.

B. The 1984 Amendments

The 1984 Amendments²⁸ acted both "to clarify the definition of 'rare disease or condition' included in the Orphan Drug Act"²⁹ and to amend Section 526 of the FDCA, making it unnecessary for drug sponsors to perform difficult calculations about the potential development and marketing costs for drugs with patient populations under 200,000. Drugs developed to treat diseases with such small populations were granted automatic consideration as orphan drugs.³⁰ If a drug had a patient pool of 200,000 or more, its sponsor would have to prove the treatment's unprofitability in order to qualify.³¹

Prior to this amendment, the high administrative burden of proving unprofitability for all orphan drugs had deterred companies from taking advantage of the Act's incentives. Senator Hatch expressed his concern over this issue to the Senate.³² While he recognized the arguments for

27. 48 Fed. Reg. 40,784 (1983). The interim guidelines dealt with both protocol assistance under § 525 of the FDCA, and with orphan designation under § 526 of the FDCA (which required that sponsors submit information dealing with the drug's profitability to determine whether the drug would recoup its development costs).

28. Health Promotion and Disease Prevention Amendments, Pub. L. No. 98-551, 98 Stat. 2817 (1984). The discussion surrounding the inclusion of a definition for "rare disease" took place in October 1984 in both Houses of Congress. In the House of Representatives, during discussions concerning the proposed Amendments of 1984, Rep. Waxman stated that:

the legislation would change the statutory definition of rare disease or condition in the Orphan Drug Act to clarify when a drug can be designated by the F.D.A. as an orphan drug. Under the amendment a drug for a disease which affects less than 200,000 people in the United States would be an orphan drug.

130 CONG. REC. H31,024 (daily ed. Oct. 9, 1984) (statement of Rep. Waxman). Rep. Waxman also stated that the Senate bill, sponsored by Senator Orrin Hatch, was in "agreement that we should not be paying the high costs to treat diseases that we know are preventable." *Id.* at H31,025.

29. 98 CONG. REC. S31,840 (daily ed. Oct. 11, 1984) (statement of Sen. Kassebaum).

30. Pub. L. No. 98-551, 98 Stat. 2817 (1984).

31. *Id.*

32. 98 CONG. REC. S31,839 (statement of Sen. Hatch):

S. 771 as passed by the House also includes an amendment designed to clear up uncertainty over the operation of the Orphan Drug Act. Under that legislation, which we passed in 1982, we gave certain incentives to drug manufacturers to induce them to shoulder the considerable developmental and regulatory costs of bringing to market drugs which would otherwise not be profitable afflicting only a relatively small portion of the population.

and against defining rare disease by patient population, Sen. Hatch stated that "the more important consideration is making the act workable [F]or now, we need to give full encouragement to the development and approval of drugs which will otherwise not see the light of day."³³

C. The 1985 Amendments

Under the 1985 Amendments,³⁴ the grant program, which allowed for grants to independent medical researchers for clinical testing, was renewed for another three years.³⁵ The Act was also amended to extend market exclusivity to orphan drugs which could be patented because patent protection was considered an insufficient incentive towards development.

[E]ven when orphan drugs have product patents, the animal and human clinical research necessary for approval often is not initiated until late in the patent term. As a result, by the time testing begins the patents have expired or soon will expire. In many other cases, the original research on the use of a drug for a rare disease is not initiated by an individual or drug company which holds an outstanding patent, but by an individual medical researcher As a result, by the time a drug company becomes interested in testing the use of the drug for the rare disease, the use can not be patented³⁶

D. The 1988 Amendments

The Amendments of 1988³⁷ reauthorized two of the Act's monetary incentives: the clinical grant programs and the clinical tax credit.³⁸ More money was allotted to extend research and development grants until the end of fiscal year 1990.³⁹ In addition, the amendments placed orphan medical foods and devices within the eligibility requirements for clinical grants. These products remained ineligible for the market

33. *Id.*

34. Orphan Drug Amendments of 1985, Pub. L. No. 99-91, 99 Stat. 387 (1985).

35. H.R. REP. NO. 153, 99th Cong., 1st Sess. (1985), reprinted in 1985 U.S. CODE CONG. & ADMIN. NEWS 301.

36. *Id.*

37. Orphan Drug Amendments of 1988, Pub. L. No. 100-290, 102 Stat. 90 (1988).

38. 21 U.S.C. § 360ee (1988) (grant program); 26 U.S.C. § 28 (1988) (tax credit).

39. 134 CONG. REC. H1018 (daily ed. Mar. 22, 1988).

exclusivity provision and tax incentives.⁴⁰ The 1988 bill also amended the Act to ensure that if a company chose to stop producing an orphan treatment, the FDA would be notified one year before the production stopped. This requirement allows the FDA time to find another manufacturer who will continue production.⁴¹

In 1988, there was also debate over whether the exclusivity provision should be amended to rectify the growing problem of windfall profits deriving from the seven years of market exclusivity. In short, while the purpose behind the Act was to "help companies reduce or avoid financial loss from orphan drug development," Congress never intended for the incentives to "shield highly profitable drugs from competition."⁴² Despite these concerns, the exclusivity provision was not modified in the 1988 Amendments.

III. THE CURRENT ACT AND RECENT PROPOSALS FOR ITS REFINEMENT

A. *The Current Act*

The Act as it has evolved provides manufacturers with several incentives to develop orphan drugs. The most attractive, and perhaps the most controversial incentive, is the seven-year grant of market exclusivity offered to the first company to receive marketing approval from the FDA for its designated orphan drug.⁴³ The exclusivity provision is essentially a seven-year monopoly, since no other manufacturer can sell the designated drug to treat a particular disease or condition, except in very rare cases.⁴⁴

The current tax credit covers fifty percent of the costs associated with

40. The grant incentive to develop medical foods and other products was a response to the growing reliance by the medical field on these items in the treatment of disease. However, the Committee was unwilling to recommend that all of the orphan drug incentives be extended to medical foods and devices. Instead, the bill required the Secretary of Health and Human Services to conduct a study to determine if such an expansion of the orphan drug law was necessary. H.R. REP. NO. 473, 100th Cong., 1st Sess. (1987), *reprinted in* 1988 U.S. CODE CONG. & ADMIN. NEWS 46, 50.

41. 134 CONG. REC. H1019 (daily ed. Mar. 22, 1988) (statement of Rep. Waxman).

42. 134 CONG. REC. S3686 (daily ed. Mar. 31, 1988) (statement of Sen. Kassebaum).

43. See 21 U.S.C. § 360cc(a) (1988).

44. See H.R. REP. NO. 635, 101st Cong., 2d Sess. (1990), § 527(b)(1)(A). The FDA can approve further drug applications if the first company cannot ensure a sufficient supply of the drug for the patient population or if the company will be stopping production of a treatment. *Id.*

clinical testing.⁴⁵ This amount can be claimed directly as a credit against the taxes owed by the drug's sponsor,⁴⁶ and thus is more favorable than a tax deduction, which is claimed against the income to be taxed. Congress also currently allocates several million dollars annually for the purpose of awarding grants to independent medical researchers to conduct clinical research on orphan products.⁴⁷

B. The Vetoed 1990 Amendments

The current Act would have been quite different if the Amendments of 1990⁴⁸ had been enacted. These amendments would have allowed market exclusivity to be revoked when a drug's population grew to more than 200,000.⁴⁹ In addition, the amendments would have provided for shared market exclusivity in limited cases where an orphan drug appeared from the beginning to be so profitable that several sponsors were racing to obtain the first approval. The FDA would have been able to approve subsequent applications of additional sponsors only if these sponsors had simultaneously developed the drug.⁵⁰ This "simultaneous development" restriction required the other manufacturers seeking approval to show that their designation, pre-clinical, and clinical investigations took place at approximately the same time as those for the first drug approved.⁵¹

C. The 1991 Proposed Regulations

During the eight-year period since the Act was passed, the FDA did not promulgate regulations concerning orphan drug designations, IND applications, or NDA approval, although these regulations were required by the Act.⁵² Until this year, the FDA had followed loose "interim guidelines," which meant that each controversy or problem that arose concerning the Act and its provisions had to be decided on a case-by-case basis. On January 29, 1991, the FDA finally published proposed regulations for implementing the Act and correcting ambiguities in the

45. 26 U.S.C. § 28 (1988).

46. 53 Fed. Reg. 38,709 (1990) (to be codified at 26 C.F.R. § 602).

47. 21 U.S.C. § 360ee(c) (1988).

48. H.R. 4638, 101st Cong., 2d Sess., 136 CONG. REC. H5799 (daily ed. July 30, 1990).

49. *Id.* § 2.

50. *Id.* § 3.

51. *Id.*

52. 21 U.S.C. §§ 360aa(b) & 360bb(d) (1988).

Act that have led to abuses.⁵³ The proposed regulations respond to many of the problems that have arisen in recent years. They outline the procedures orphan drug sponsors should use to avail "themselves of the incentives provided for in the Orphan Drug Act and set forth the procedures FDA will use in administering it."⁵⁴ The FDA stated that the proposed regulations are "intended to benefit consumers by encouraging manufacturers to develop and make available to patients drugs for diseases and conditions that are rare in the United States."⁵⁵ Thus, the regulations embody the purposes of the original Act.

Specifically, the regulations facilitate the development of new orphan drugs by: (1) establishing a procedure for sponsors to request assistance from the FDA in planning protocols for pre-clinical and clinical studies;⁵⁶ (2) elaborating the procedure for requesting orphan drug designation and describing the format and content required for the application;⁵⁷ and (3) allowing "a sponsor to provide a [designated] investigational drug product under a treatment protocol to patients who need the drug for treatment of a rare disease or condition."⁵⁸ The regulations also propose a number of steps to prevent abuses of the Act. Among these is a provision for refusing a request for written recommendations if it contains an untrue statement of material fact.⁵⁹ An application for designation may also be refused if the company has omitted or misrepresented facts.⁶⁰ The sponsor is required to submit documentation that its drug satisfies the orphan drug criteria for designation,⁶¹ and the FDA may examine a sponsor's books to verify the financial data submitted, if the sponsor requests orphan status for a drug because of "non-recoverability of costs."⁶² The agency would also be able to suspend or revoke exclusivity if the drug in fact had not been eligible for orphan drug designation when the application was submitted.⁶³ The regulations contain additional provisions that ensure continuous availability of an orphan drug. Market exclusivity can be revoked if the holder cannot produce enough of a supply to reach the patient population, or has

53. 56 Fed. Reg. 3338 (1991).

54. *Id.*

55. *Id.*

56. *Id.* at 3346-48 (to be codified at 21 C.F.R. § 316.10-14).

57. *Id.* at 3348 (to be codified at 21 C.F.R. § 316.20).

58. *Id.* at 3345 (to be codified at 21 C.F.R. § 316.1(a)(2)). *See also id.* at 3351 (to be codified at 21 C.F.R. § 316.40).

59. *Id.* at 3347 (to be codified at 21 C.F.R. § 316.14(a)(6)).

60. *Id.* at 3349 (to be codified at 21 C.F.R. § 316.25(b)).

61. *Id.* at 3348.

62. *Id.* at 3349 (to be codified at 21 C.F.R. § 316.21(d)).

63. *Id.* at 3350 (to be codified at 21 C.F.R. § 316.29(a)(3)).

notified the FDA that it will be stopping production of an approved orphan treatment.⁶⁴ Before market exclusivity is revoked for this reason, the Director of FDA's Office of Orphan Products Development must notify the holder of the possible insufficiency of supply, and must offer the holder one of two options: (1) prove that the company can ensure availability of sufficient supplies, or (2) consent to approval of other NDAs for the same drug.⁶⁵ The proposed regulations also define whether drugs are to be considered the same or different for approval purposes. This definition comes in response to recent controversies over whether a variant of a drug which currently holds market exclusivity can be approved.⁶⁶ This aspect of the regulations is discussed in Section V in greater detail.

IV. ABUSE OF THE MARKET EXCLUSIVITY PROVISION

The seven-year monopoly granted by the market exclusivity provision of the Act is considered by pharmaceutical manufacturers to be the Act's most important incentive.⁶⁷ The provision is effective because it enhances the profitability of otherwise unprofitable orphan drugs. However, it can be abused when companies obtain market exclusivity for highly profitable drugs that do not need orphan protection. There has been much controversy over some of these drugs, which have development costs in the tens of millions of dollars, but annual sales in the hundreds of millions.⁶⁸ The abuse of this provision can take a variety of forms: A drug that originally qualified as an orphan may subsequently outgrow orphan criteria because of changed circumstances; a drug that is very profitable may technically qualify as an orphan because its target population is less than 200,000 persons; a pharmaceutical manufacturer may try to squeeze its drug into the orphan category by artificially decreasing the drug's target population; or a company may mislead the FDA in its applications for orphan designation. However, none of these problems are insurmountable. The remainder of this Section discusses these problems in greater detail and suggests how they can be solved by

64. *Id.* at 3351 (to be codified at 21 C.F.R. § 316.36); see *supra* note 44 and accompanying text.

65. *Id.* (to be codified at 21 C.F.R. § 316.36(a)).

66. *Id.* at 3338 (to be codified at 21 C.F.R. § 316.3(b)(13)(ii)(a)).

67. NATIONAL COMM'N ON ORPHAN DISEASES, U.S. DEPT' OF HEALTH & HUMAN SERVICES, REPORT OF THE NAT'L COMM'N ON ORPHAN DISEASES 8 (1989) [hereinafter COMMISSION REP.].

68. See *infra* text accompanying notes 94-97.

fine-tuning the Act with appropriate legislation, like that proposed in the vetoed 1990 Amendments, and by implementing and refining the proposed regulations.

A. *Drugs that Outgrow the Orphan Criteria*

1. *Increased Target Population*

A drug automatically qualifies for orphan status if its target population is less than 200,000. However, its target population could grow to exceed that limit. For example, the number of persons with Acquired Immunodeficiency Syndrome ("AIDS") is constantly increasing, and will eventually exceed 200,000, if it has not already. AIDS drugs such as azidothymidine ("AZT") and pentamidine are highly profitable, and their inflated prices have stirred much controversy and protest. AZT has estimated annual sales of \$180 million.⁶⁹ After widespread protest by consumers, Burroughs-Wellcome lowered the drug's price from \$8200 to \$6500 per year.⁷⁰ Pentamidine, with annual sales of \$128 million in 1989,⁷¹ retails at \$26 a vial in Europe, but retails at from \$120 to \$200 a vial in the United States.⁷²

Under the current Act, market exclusivity is not revocable when the drug's target population grows to more than 200,000.⁷³ This would have been changed by Section 2 of the Orphan Drug Act Amendments of 1990⁷⁴ that the President pocket vetoed last fall. This section provided for withdrawal of a drug's market exclusivity if its target population rose above 200,000.⁷⁵ Unlike the other sections,⁷⁶ this withdrawal would have applied retroactively to drugs that had already been approved.

The President's Memorandum of Disapproval expressed concern that this provision would weaken the Act's market incentives, and that the "retroactive rule change would send a troublesome signal to all those who might wish to develop orphan drugs that the Federal Government

69. Carey & Hamilton, *These 'Orphans' Don't Need Any Nurturing*, BUS. WK., July 2, 1990, at 38.

70. The cost of AZT treatment was reduced further to as little as \$2200 per year when the recommended dosage was reduced. N.Y. Times, Dec. 6, 1990, at A1, col. 1.

71. Ashbury, *The Orphan Drug Act, The First 7 Years*, 265 J. AM. MED. A. 893, 896 (1991).

72. N.Y. Times, Jan. 10, 1991, at B9, col. 1.

73. 56 Fed. Reg. 3338, 3350 (1991) (to be codified at 21 C.F.R. § 316.29).

74. H.R. 4638, 101st Cong., 2d Sess., 136 CONG. REC. H5799 (daily ed. July 30, 1990).

75. *Id.*

76. See *infra* text accompanying notes 103-06.

may change unilaterally the rules for firms that made investment decisions based on the expectation of 7 years of market exclusivity."⁷⁷

The Memorandum exaggerates the impact of the provision. Few rare disease populations undergo substantial growth, and even fewer will outgrow the 200,000 limit.⁷⁸ However, the proposed amendments were wrong to focus on the arbitrary 200,000 population limit, because a drug which outgrows this limit might still be an unprofitable orphan. The proposed amendments for revocation should have allowed a drug to retain its orphan designation if it satisfied the alternative criterion for approval, of "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."⁷⁹ If the drug is truly an orphan, the company will be able to prove this. If not, then the drug should not be protected by the Act.

2. Expanded Treatment Indications

A drug may become useful for treating conditions other than the original rare disease or condition, thus effectively increasing its target population. For example, the orphan drug human growth hormone ("HGH") was designated for treating hypopituitary dwarfism, but is now used to treat other growth hormone disorders,⁸⁰ and may be useful for treating severe burns and osteoporosis.⁸¹ A recent study on men has even found that growth hormone may reverse the effects of aging.⁸² As another example, the orphan drug erythropoietin was designated for treating patients on chronic dialysis, but it can also be used to treat any patients with anemia, such as cancer or AIDS patients.⁸³ It may even be used, illegally, for improving athletes' performance.⁸⁴

A manufacturer whose drug holds market exclusivity for one rare disease has no incentive to go through an expensive approval process for

77. 137 CONG. REC. H73 (daily ed. Jan. 3, 1991).

78. In fact, most rare diseases do not even approach that limit. Ninety-four percent of the 123 orphan drugs designated in the first three years of the Act have target populations of less than 100,000. Richardson, *The Orphan Drug Tax Credit: An Inadequate Response to an Ill-Defined Problem*, 6 AM. J. TAX POL'Y 135, 177 (1987).

79. 21 U.S.C. § 360bb(a)(2)(B) (1988) (approval of orphan drug status).

80. *Human Growth Hormone: Little Big Drug*, ECONOMIST, Oct. 6, 1990, at 102.

81. N.Y. Times, Nov. 9, 1990, at A16, col. 1.

82. L.A. Times, Dec. 28, 1990, at E2, col. 4.

83. See *Ortho Pharmaceutical Co. v. Amgen*, 709 F. Supp. 504, 506 (D. Del. 1989). According to Dr. Wayne Turner at the FDA Office of Orphan Products Development, erythropoietin has recently been approved for treating anemia in AIDS patients. Conversation with Dr. Wayne Turner, Pharm. D., Reviewing Pharmacy Officer (Feb. 28, 1991).

84. USA Today, Sept. 11, 1989, at C1.

new non-rare disease indications. In fact, approval of an orphan drug for a non-rare disease indication would effectively cancel out orphan market exclusivity in many situations, because the orphan drug would then face competition from generic versions.⁸⁵ An orphan drug can still be used for a new non-rare disease indication, even without FDA approval, because physicians have discretion to prescribe drugs for non-approved conditions.⁸⁶ Only the manufacturer is precluded from promoting a non-approved use.⁸⁷ Thus, an orphan drug manufacturer can potentially gain a windfall profit from the new use without ever investing in FDA approval for that use.

However, the scope of this problem is limited. An orphan drug with new uses may initially gain a windfall profit, but if the new market is large enough to be profitable, other pharmaceutical companies will invest in approval for the new indications. Since an orphan drug is designated and approved for a specific rare disease, the exclusivity provision of the Act does not prevent a second company from getting the same drug approved for a different disease, or for a different subset of the target population.⁸⁸

3. *Unexpected Profitability*

A drug with a target population of 200,000 or more can be designated as an orphan if there is no reasonable expectation that its development

85. Market exclusivity does not protect the approval of an unpatented orphan drug for a non-rare disease indication; thus, upon approval for such an indication, an unpatented orphan drug will face competition from low-priced generic versions which are approved for the non-rare disease. This will be true in many situations, since a substantial number of orphan drugs are unpatentable. H.R. REP. NO. 840(I), *supra* note 3, at 3579. Although the generic versions cannot be approved for the rare disease indication, because of the market exclusivity status of the pioneer orphan drug, they may still be prescribed for the rare disease. *See infra* text accompanying notes 86–87. 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 NDA. 21 C.F.R. § 314.55 (1990). All that is required are bioavailability studies, which are relatively simple and much less expensive than the detailed pre-clinical and clinical investigations required for a full NDA. *See* 21 C.F.R. § 320.21–31 (1990).

86. Thomas, *Re-Assessing the Orphan Drug Act*, 23 COLUM. J.L. & SOC. PROBS. 413, 429–30 (1990) (citing L. MILLSTEIN, DRUG PRODUCT LABELING IN NEW DRUG APPROVAL PROCESS 330 (1987)). However, third party payors such as insurance companies may refuse reimbursement for drugs used for non-approved conditions. Conversation with Dr. Turner at the FDA (Feb. 28, 1991).

87. 21 C.F.R. § 201.2(c)(4) (1990).

88. *See* 56 Fed. Reg. 3338, 3339 (1991); *see also* H.R. REP. NO. 153, 99th Cong., 1st Sess. (1985), *reprinted in* 1985 U.S. CODE CONG. & ADMIN. NEWS 301.

costs will be recovered from sales.⁸⁹ Such a drug could unexpectedly become very profitable if its market becomes larger than predicted, or if the market bears higher prices than anticipated.

It is unclear what will happen in this situation. The FDA has the authority under its proposed regulations to "suspend or revoke orphan drug designation for any drug if the . . . FDA subsequently finds that the drug in fact had not been eligible for orphan drug designation at the time of the submission of the request therefor."⁹⁰ The final regulations should clarify this ambiguous standard. One interpretation is that market exclusivity should be revoked only if large profits make it obvious that previous sales projections were unreasonably low. Another is that exclusivity should be withdrawn when it is evident that the company has recouped its development costs.⁹¹

B. Highly Profitable Drugs that Technically Qualify for Orphan Status

The 1984 Amendments replaced the vague "non-recovery of costs" criterion with a "bright line" criterion of "less than 200,000 affected persons" to minimize the administrative burden of proving orphan status.⁹² The limit was purposely set at a very high level, to encourage rather than inhibit the development of orphan drugs. However, this bright line rule is both underinclusive and overinclusive. It is underinclusive because some drugs that are excluded by the rule may still be unprofitable "orphans," and it is overinclusive because some included drugs may be highly profitable.

The Act solves this underinclusiveness problem by allowing non-included drugs to be designated as orphans if their development costs are not expected to be covered by sales.⁹³ There is no such fine-tuning for the overinclusiveness problem. Thus, some very profitable drugs that do not deserve orphan status will necessarily be included in the orphan

89. 21 U.S.C. § 360bb(a)(2)(B) (1988). Very few, if any, drugs with target populations of more than 200,000 have been designated as orphan drugs under subsection B. According to Dr. Turner at FDA's Office of Orphan Products Development, to the best of his knowledge there have been no drugs designated under this subsection. Conversation with Dr. Turner (Feb. 28, 1991).

90. 56 Fed. Reg. 3338, 3350 (to be codified at 21 C.F.R. § 316.29(a)(3)).

91. Since a drug in this orphan category is defined as a drug for which there is no reasonable expectation that development costs will be recovered from sales, technically the drug is not an orphan when development costs have been recovered. However, this view is debatable.

92. 21 U.S.C. § 360bb(a)(2)(A) (1988). See also *supra* notes 28-33 and accompanying text.

93. 21 U.S.C. § 360bb(a)(2)(B) (1988).

category because their target population is less than 200,000. The large profits come from the extremely high prices paid by rare disease sufferers and the government. For example, HGH costs \$10,000 to \$30,000 per patient and has estimated annual sales of more than \$175 million;⁹⁴ erythropoietin costs \$8000 per patient and has estimated annual sales of more than \$200 million, most of which comes from Medicare;⁹⁵ AZT has estimated annual sales of \$180 million.⁹⁶ These figures represent very high returns on investment. Development costs for HGH are reported at \$35 million for Genentech's version, and \$17 million for Eli Lilly's version.⁹⁷ Pentamidine sales were \$128 million in 1989 and are projected to be \$480 million in 1990; the drug cost only \$23 million to develop and will cost \$15 to \$20 million more for post-marketing studies.⁹⁸

One proposed solution is an orphan drug windfall tax. Rep. Stark introduced a bill⁹⁹ last year that would have imposed a seventy-five percent tax on windfall profits, defined as those revenues exceeding a twenty-five percent profit.¹⁰⁰ He described the bill as follows:

[A] pharmaceutical company would be able to recapture two times its developmental costs, and generate not more than 25 percent annual profit off of its orphan drug before the [75 percent] windfall tax would go into effect. The figure of 25 percent [was] chosen because it is a comfortable estimate of the average market profit for the brand prescription drug industry.¹⁰¹

The bill would also expand the tax credit incentives by including pre-clinical testing in the covered research expenses.

Although a windfall tax is theoretically a good idea, it places a high initial and ongoing administrative burden on all orphan drug manufacturers to calculate developmental, production, and marketing costs.

94. 136 CONG. REC. H5800 (daily ed. July 30, 1990) (statement of Rep. Waxman).

95. *Id.*

96. Carey & Hamilton, *supra* note 69, at 38.

97. Ashbury, *supra* note 71, at 896.

98. *Id.*

99. H.R. 5421, 101st Cong., 2d Sess. (1990).

100. *Id.* §3. Windfall profit was defined as the amount by which a drug's gross sales revenues for a particular year exceeded 125% of the drug's production and allocable marketing costs for that year. This windfall profit was to be taxed at a 75% rate, but the tax would not take effect until the company had recovered twice the amount of the drug's development costs.

101. 136 CONG. REC. H6194 (daily ed. July 31, 1990) (discussing H.R. 5421) (statement of Rep. Stark).

Concern over a similar administrative burden led to the 1984 Amendments which eliminated the "non-recovery of costs" calculations previously required for designation.¹⁰² In addition, a less-than-100% windfall tax gives the manufacturer an incentive to continue to overcharge and in some cases may even cause the company to pass the extra tax onto the consumer.

The vetoed 1990 Orphan Drug Amendments¹⁰³ proposed another solution. The amendments would have provided for shared exclusivity in limited situations where two or more companies simultaneously developed an orphan drug because it was predicted from the start to be highly profitable.¹⁰⁴ Another company could qualify for simultaneous development of an orphan drug if it (1) applied for orphan designation within six months of the publication date of the first company's orphan designation; (2) started human clinical trials within twelve months of the pioneer company; and (3) applied for drug approval within twelve months of the pioneer company.¹⁰⁵ The bill would have "grandfathered" orphan drugs which had already been approved or which were still undergoing human clinical trials.¹⁰⁶

The President's Memorandum of Disapproval stated that "we must not endanger the success of this program, which is due [in] large measure to the existence of the 'market exclusivity' provision Weakening the current 7-year exclusivity provision would certainly discourage development of desperately needed new orphan drugs."¹⁰⁷ The veto was a surprise because the amendments were the product of a number of compromises, were supported by industry and patient advocacy groups, and were passed unanimously.¹⁰⁸ The original version would have been much tougher on profitable orphan drug manufacturers since it lacked both the strict three-part definition of simultaneous development and the "grandfather" clause.¹⁰⁹ It was modified in response to objections that "follow-on" companies could obtain shared exclusivity by copying the work of the pioneer company, and that retroactivity would hurt

102. See *supra* text accompanying notes 28-33.

103. H.R. 4638, 101st Cong., 2d Sess., 136 CONG. REC. H5799 (daily ed. July 30, 1990).

104. *Id.* § 3. In the cases of such highly profitable drugs as HGH, erythropoietin, and pentamidine, there were two or more companies that completed full clinical trials and submitted NDAs in a race for approval. H.R. REP. NO. 635, *supra* note 44. In fact, there were five companies racing for HGH approval. See *infra* note 118.

105. *Id.* § 3(a)(2).

106. *Id.* § 3(a)(2)(A).

107. 137 CONG. REC. H73 (daily ed. Jan. 3, 1991).

108. N.Y. Times, *supra* note 81, at A16.

109. H.R. 4638, 101st Cong., 2d Sess., draft version 1, May 1, 1990.

companies that had invested in orphan drugs with expectations that the law not be altered.¹¹⁰

Rep. Waxman plans to introduce a version of the 1990 amendments that is closer to the original than the compromise version.¹¹¹ This would present an excellent opportunity to pass a stronger, more effective bill. The "grandfather" clause should be deleted; it exempts 175 orphan drugs, including those still in human clinical trials, from the effect of the amendments.¹¹² Since it will take years for many of these drugs to be approved, lower-priced generic versions may not be available for a decade or more. Until that time, the costs of high-priced orphan drugs will continue to be borne by their consumers, who include not only rare-disease sufferers but also government programs, such as Medicare¹¹³ and Medicaid, which pay for such drugs.

Some sort of amendment is necessary to fine-tune the Act and prevent excessive profits for orphan drug manufacturers. In situations where multiple companies simultaneously develop an orphan drug, shared exclusivity would provide a moderate amount of competition that could be beneficial for consumers. The presence of many drug companies racing for approval of an orphan drug is a good indication that the drug is profitable and should not be given full orphan protection. The simultaneous development requirement for shared exclusivity would reduce the number of companies sharing in the monopoly, and ensure that the second companies are not attempting to copy a pioneer company's work.

While Rep. Waxman's amendment would slightly weaken the Act's market incentives, it would probably not lead to a flood of cutthroat competition. Each of the competing manufacturers would have invested comparable sums in research and development, and generic versions of the drug would still be excluded from the market.¹¹⁴ However, it is possible that the perception of weakened incentives could inhibit investment

110. 136 CONG. REC. H11,931 (daily ed. Oct. 23, 1990) (statement of Rep. Scheuer). Some might object to the retroactivity as a taking of property. However, it is unclear whether market exclusivity is a property right. The FDA's position is that "[t]he seven-year period of exclusive marketing is not a property right but is a prohibition against action by FDA." Letter from John Taylor, FDA Associate Commissioner for Regulatory Affairs, to Patricia J. Kenney, Esq., Senior Corporate Counsel, Genentech, Inc. (Mar. 6, 1987).

111. Conversation with staff member of Health and Environment Subcommittee (Feb. 1, 1991).

112. See *supra* note 7 and accompanying text.

113. Most of Amgen's \$200 million sales revenues came from Medicare. See *supra* text accompanying note 95.

114. In order for a manufacturer to obtain shared exclusivity, it would have to complete full clinical trials and submit an application for drug approval. See *supra* text accompanying note 105.

in orphan drugs.¹¹⁵ This concern could be addressed by strengthening a different aspect of the Act's incentives, such as tax credits.¹¹⁶ Alternatively, the seven-year term of marketing exclusivity could be lengthened in those cases where exclusivity is shared by two or more companies.¹¹⁷

The proposed amendments may actually encourage smaller companies, such as biotechnology start-ups, to invest in orphan drugs. Under the current Act, a runner-up company that has invested a great deal of money in the approval process is completely closed out of the benefits when it loses the race.¹¹⁸ The company may not have known until too late that it was entering a race, because applications for orphan designation are secret until the drugs are designated,¹¹⁹ and because companies frequently do not apply for designation until after human clinical trials have started. The risk of losing a substantial investment, which is proportionally higher for smaller companies, may deter them from investing in orphan drugs. Shared exclusivity would decrease some of the risks of development in a secret environment, while preserving sufficient market profitability.

115. The Pharmaceutical Manufacturers Association felt that the Act would no longer be effective if shared exclusivity were implemented, but reluctantly supported the compromise amendment. Gibbons, *Billion-Dollar Orphans: Prescription for Trouble*, 248 SCI. 678, 679 (1990).

116. The National Commission on Orphan Diseases ("Commission") has recommended that tax credits be expanded to all developmental activities, not just clinical studies. See *infra* note 166. An expansion in tax credits is unlikely, given the current budgetary situation. However, if the tax credit expansion and the shared exclusivity were implemented together, the lost tax revenue might be recouped from savings in Medicare and Medicaid expenditures for exclusively-priced orphan drugs. For example, the one-time cost to Amgen of developing erythropoietin was \$170 million, 136 CONG. REC. H6194 (daily ed. July 31, 1990) (statement of Rep. Stark), part of which was probably recouped through existing tax credits, while its annual revenue of \$200 million came mostly from Medicare, see *supra* note 113. See also *infra* note 167 regarding tax credits.

117. The Commission has recommended that the term of exclusivity be lengthened, see COMMISSION REP., *supra* note 67, at 58, to strengthen market incentives. However, the incentive boost from the extended exclusivity should be balanced against the burden to consumers of the longer time period before low-cost generic versions become available.

118. Five companies spent millions of dollars in a race to gain approval for a 191-amino acid version of HGH. Eli Lilly's NDA, submitted only six weeks ahead of another company's NDA, won the race. The other four companies lost their entire investments, including opportunity costs. Kenney, *The Orphan Drug Act—Is it a Barrier to Innovation? Does it Create Unintended Windfalls?*, 43 FOOD, DRUG, COSMETICS L.J. 667, 675-77 (1988).

119. 56 Fed. Reg. 3338, 3351 (1991) (to be codified at 21 C.F.R. § 316.52(a)).

*C. Drugs that Are Artificially Squeezed into
the Orphan Category*

A company may attempt to qualify a drug for orphan designation by creating artificial subsets of the total patient population, thus making the drug's target population appear to be less than 200,000. For example, erythropoietin has a variety of potential uses, including the treatment of patients on chronic dialysis, patients with anemia caused by early, pre-dialysis kidney problems, and patients with anemia caused by cancer or AIDS. Yet this drug was designated only for treating chronic dialysis patients.¹²⁰ "The practice has gotten so absurd, the FDA reports, that one company tried—and failed—to get orphan status for a drug to relieve knee pain. Left knee pain."¹²¹

The FDA has addressed this problem in its proposed regulations¹²² by requiring an applicant for orphan designation to demonstrate that the subset of a patient population to be treated with the drug is medically plausible. In the memorandum accompanying the regulations, the FDA specifies that the designation application is subject to review by the Center for Drug Evaluation or the Center for Biologics Evaluation and Research, and that these centers will consider in their reviews whether the target populations have been artificially restricted.¹²³

D. Misleading Applications for Orphan Designation

A company that wishes to gain orphan drug protection for a highly profitable drug may be tempted to omit or misrepresent facts in its application for designation. The FDA contemplated this problem in its proposed regulations. It can punish a company for this type of abuse by refusing an application for designation,¹²⁴ or by suspending or revoking a designation.¹²⁵ Suspension or withdrawal of designation also suspends or revokes the market exclusivity privileges.¹²⁶ A company that is requesting orphan drug designation for a drug which treats 200,000 or more persons must have its estimates verified by an independent accountant, and must allow the FDA to examine its books to verify its

120. See *Ortho Pharmaceutical Co. v. Amgen*, 709 F. Supp. 504, 506 (D. Del. 1989).

121. Carey & Hamilton, *supra* note 69, at 38.

122. 56 Fed. Reg. 3338, 3339-40 (1991) (to be codified at 21 C.F.R. § 316.20).

123. *Id.* at 3339.

124. *Id.* at 3350 (to be codified at 21 C.F.R. § 316.25(b)).

125. *Id.* (to be codified at 21 C.F.R. § 316.29(a)).

126. *Id.* (to be codified at 21 C.F.R. § 316.29(b)).

financial data.¹²⁷

This should be an effective deterrent to misrepresentation. Others have proposed open hearings for designation, reasoning that challenges from competitors will keep companies honest,¹²⁸ but this seems unnecessary and difficult to implement since information in the application must be kept confidential.¹²⁹

V. DEFINITION OF THE SCOPE OF MARKET EXCLUSIVITY

The FDA provides market exclusivity protection for a pioneer drug by staying approval of all NDAs for the "same" drug until the seven-year period of exclusivity expires.¹³⁰ However, if the agency considers two variants of a drug to be "different," regardless of how similar the two are, it may approve NDAs for both drugs. For example, Genentech received the first orphan drug approval for HGH. Eli Lilly later obtained approval for a second version of HGH that differed from Genentech's by only one amino acid.¹³¹ The FDA also approved two versions of alpha interferon that differ by a single amino acid.¹³²

A company may try to force its way into the market for an approved orphan drug by applying for orphan designation on a variant of the pioneer drug. This is especially problematic for biotechnology companies, because minor variants of their genetically engineered products can be made very easily. Until detailed regulations were proposed, the definition of a "different" drug was unclear and controversies were decided on a case-by-case basis.

The FDA has proposed a fairly reasonable standard to govern whether drugs will be considered the "same" or "different" for purposes of orphan designation and drug approval. "Same" is defined in proposed regulation Section 316.3(b)(13).¹³³ In the case of small molecules, which are the majority of pharmaceuticals, a drug is considered the same if it contains the same active moiety and is intended for the same use as the pioneer drug.¹³⁴ In the case of macromolecules, which include the majority of biotechnological products, a drug is considered the same if it

127. *Id.* at 3349 (to be codified at 21 C.F.R. § 316.21(d)).

128. Thomas, *supra* note 86, at 438.

129. 21 C.F.R. §§ 20.21, 20.61 (1990).

130. *See supra* text accompanying note 44. *See also* Kenney, *supra* note 118, at 677.

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

132. Kenney, *supra* note 118, at 673.

133. 56 Fed. Reg. 3338, 3346 (1991).

134. *Id.* (to be codified at 21 C.F.R. § 316.3(b)(13)(i)).

has the same principal molecular structural features as the pioneer drug.¹³⁵

For proteins, which have generated the most controversy,¹³⁶ the proposed regulation specifically states that two proteins are the same if their differences are "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 are shown to be clinically superior."¹³⁷

The plain meaning of this proposed regulation appears to be that a variant of an orphan drug has the opportunity to prove clinical superiority only if it has potentially important structural differences, such as differing glycosylation patterns or tertiary structure. The language also seems to imply that a drug does not have an opportunity to prove superiority if its differences are due to post-translational events, infidelity of translation or transcription, or minor amino acid sequence changes.¹³⁸ The memorandum accompanying the proposed regulations states:

This criterion makes a presumption of sameness . . . in the face of minor differences in structure . . . even in the face of amino acid sequence differences if they are "minor." Determining whether differences in amino acid sequences should be considered minor involves judgment and could lead to legal challenges of FDA decisions.¹³⁹

135. *Id.* (to be codified at 21 C.F.R. § 316.3(b)(13)(ii)).

136. Genentech, which already had market exclusivity for Protropin, a 192-amino acid version of HGH, filed a citizen's petition with the FDA protesting the agency's grant of market exclusivity to Lilly's 191-amino-acid HGH. "Genentech took the position that Lilly's drug was, for the purposes of the Orphan Drug Act, the same as Protropin and therefore ineligible for marketing approval until 1992," when Protropin's market exclusivity would expire. *Genentech v. Bowen*, 676 F. Supp. 301, 307. The protein erythropoietin has also been the subject of controversy at the FDA; Genetics Institute and its marketing partner Chugai-Upjohn attempted to persuade the agency that their version of the drug is different from Amgen's pioneer drug, and therefore can be granted market exclusivity. See *CHEMICAL WK.*, Jan. 23, 1991, at 13. See also *supra* notes 104, 118; text accompanying notes 131-32.

137. 56 Fed. Reg. 3338, 3346 (1991) (to be codified at 21 C.F.R. § 316.3(b)(13)(ii)(A)).

138. It is interesting to note that under these new rules, the FDA would probably not have decided that Lilly's 191-amino acid version of HGH was different from Genentech's 192-amino acid version, since the benefits of the single amino acid difference were indeterminate. See *Kenney, supra* note 118, at 670 n.12.

139. 56 Fed. Reg. 3338, 3342 (1991).

Overall, the chosen criterion will probably be effective in allowing innovation while discouraging competitors from attempting to designate minor variants of a pioneer orphan drug. It will also preclude claims that two proteins translated from the same DNA sequence are different simply because of the normal heterogeneity inherent in protein production. However, the presumption of "sameness" when there are minor structural differences could be overinclusive, preventing the approval of some truly "different" drugs that have only minor differences.

This overinclusiveness is partially solved by the "clinically superior" exception, which will allow the presumption of sameness to be overcome when there are "potentially important" differences in molecular structure. However, it is troubling that drugs with differences due to post-translational events and minor amino acid sequence changes are excluded from the opportunity to prove clinical superiority. Such "minor" changes can have a significant effect on biological activity,¹⁴⁰ and thus should also be included in the category of differences which may be proven clinically superior. In fact, the regulations themselves seem to make this point. Glycosylation is a post-translational event that is specifically mentioned in the regulations as a potentially important difference subject to the "clinically superior" exception,¹⁴¹ yet the broader category of post-translational events is not considered a potentially important difference.

It should be noted that the FDA considered but rejected an alternative criterion of whether the structure of the macromolecules "differed in ways that could reasonably be expected to influence relevant pharmacologic activity."¹⁴² Although this standard is scientifically more accurate, it would have been extremely difficult to prove unless expensive clinical studies were conducted. In addition, determinations under this standard would have involved greater judgment and discretion from FDA officials.

The agency also considered the alternative approach of "allowing any evidence of structural difference, or uncertainty about structure, to cause two drugs to be considered different."¹⁴³ It rejected this approach because it would have greatly weakened the market exclusivity for

140. For example, a single change in amino acid transforms a normal hemoglobin molecule into the hemoglobin responsible for sickle cell anemia. This single amino acid change might be considered "minor," yet it causes a dramatic difference in function. Wash. Post, Jan. 30, 1990, at Z21. Some proteins require post-translational processing, such as glycosylation, in order to function properly. *Biotechnology Newswatch*, Feb. 1, 1982, at 1.

141. See *supra* text accompanying note 137.

142. 56 Fed. Reg. 3338, 3342 (1991).

143. *Id.* at 3342-43.

macromolecules.¹⁴⁴ With this scheme, "follow-on" companies would have had no difficulty in gaining approval for multiple variants of a pioneer drug, thus destroying the effectiveness of the market exclusivity for the pioneer drug.

The FDA says that it intends a liberal policy of designation but a tough standard of approval.¹⁴⁵ A second, similar drug may be designated upon a plausible showing of expected clinical superiority, but it will not be approved unless it actually demonstrates this superiority. The "FDA proposes to place the burden of proof (including the burden of production of evidence and the burden of persuasion of FDA) on the sponsor of the subsequent drug who is contending that its drug is different."¹⁴⁶

Clinical superiority is clearly defined: A second drug is superior if it is (1) more effective, (2) safer, or (3) otherwise makes a major contribution to patient care,¹⁴⁷ such as providing an oral form of a drug that is usually administered intravenously.¹⁴⁸ This is an appropriate policy because it promotes research on safer or more effective versions of a drug that would otherwise be chilled by the presumption of "sameness."

The agency has decided not to propose an administrative procedure for challenging the scope of exclusive approval or orphan designations. Its view is that "[n]either the Constitution, nor the Administrative Procedure Act, nor the Orphan Drug Act requires a hearing Hearings are time-consuming and resource-intensive. FDA is not persuaded that a regulatory hearing before the agency . . . is more likely to lead the agency to a correct result than is careful administrative review."¹⁴⁹ The FDA notes that "if a challenging sponsor has sufficient information, it can, under current regulations, mount an effective challenge to an incipient drug approval by filing a citizen petition pursuant to 21 CFR 10.30."¹⁵⁰ Unfortunately, a sponsor cannot mount such a challenge

144. *See id.* at 3342.

145. *Id.* at 3340.

146. *Id.* at 3343.

147. *Id.* at 3346 (to be codified at 21 C.F.R. § 316.3(b)(3)).

148. *Id.* at 3343.

149. *Id.* at 3344.

150. *Id.* Any interested person can initiate administrative proceedings by petitioning the Commissioner of the FDA to take, refrain from taking, or reconsider an action. 21 C.F.R. §§ 10.25, 10.30, 10.33, 10.35 (1990). Several companies have taken advantage of this; on Nov. 3, 1986 Genentech filed a citizen petition in an effort to dissuade the FDA from approving Lilly's HGH variant. *See Genentech v. Bowen*, 676 F. Supp. 301, 306 (D.D.C. 1987). Genetics Institute and Chugai-Upjohn filed citizen petitions challenging the orphan drug status of Amgen's brand of erythropoietin, 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. *Biotechnology Newswatch*, Jan. 21, 1991, at 2.

unless it has "sufficient information." Since the information in new drug applications is kept secret until approval,¹⁵¹ companies will not always have the information necessary to file a citizen petition.

At least some members of Congress consider the market exclusivity privilege to be a property right requiring due process.¹⁵² If so, the pioneer company's interest in its property rights must be balanced against the possibility that a complicated procedure for administrative challenge will be abused to delay approval of competing drugs that truly deserve approval, and against the second company's rights to confidentiality of the information in its drug application.¹⁵³ A compromise between the conflicting interests might be a bare minimum of procedure that gives notice to affected parties and allows them an opportunity to comment. Even if market exclusivity is not considered a property right, it can still be argued that the original holder of market exclusivity should be notified and allowed to comment. The FDA's proposed regulations allow for a notice and reply procedure when it is considering revoking a drug's exclusivity due to a company's inability to assure adequate supply.¹⁵⁴ By analogy, the FDA should allow a similar procedure when it is considering an action, such as approval of a variant of a drug, which will affect that drug's market exclusivity.

VI. REMAINING BARRIERS TO THE EFFECTIVENESS OF THE ACT

Despite the problems discussed above, abuses of the Act are limited to a few highly visible and lucrative drugs. The Orphan Drug Act has done a great deal to encourage the development of over 100 orphan drugs. However, orphan treatments are still unavailable to the vast majority of those who suffer from the more than 5,000 rare diseases. Some barriers to orphan drug development remain, such as the

151. Confidentiality is required by 21 C.F.R. §§ 20.21, 20.61 (1990).

152. See 136 CONG. REC. H11,931 (daily ed. Oct. 23, 1990) (statement of Rep. Scheuer) ("many Members of the House rightly objected to the feature of the bill that retroactively took away the market exclusivity property right held by companies"). See also *id.* (statement of Rep. Richardson) ("the legislation might be unconstitutionally perpetrated a taking of private property [sic]"); 136 CONG. REC. S16,844 (daily ed. Oct. 23, 1990) (statement of Sen. Simon) (under the proposed amendments to withdraw exclusivity for drugs which outgrow the 200,000 person limit, if a company's market exclusivity were challenged by another company or by the FDA, "the affected company would be given a meaningful opportunity to present its own data and arguments on this issue. In my view, due process, and fundamental fairness to those whose businesses may be affected, require nothing less."). However, this issue is debatable. See *supra* note 110.

153. See *supra* note 151.

154. 56 Fed. Reg. 3338, 3351 (1991) (to be codified at 21 C.F.R. § 316.36).

uncertainty of the Act's market incentives, the weakness of the tax credit incentive, the long and arduous drug approval process, the possibility of liability, and the lack of funds for basic scientific research. The Act could become even more effective if these impediments were removed.

A. *The Uncertainty of the Act's Market Incentives*

Because the application for orphan designation is kept secret until it is approved, and companies often do not apply for designation until clinical trials have started, a company may not realize until too late that it is in a race with another company for orphan drug approval. Since the race is won by the date of NDA approval, rather than the date of designation, and since neither company knows if it is ahead in drug testing, both companies may decide to continue competing in hopes of recouping their already-committed investment. Such a contest is unproductive in a market which, by definition, is unprofitable. The 1990 Amendments, which made the designation date an important criterion for shared exclusivity, would have had the beneficial effect of encouraging companies to apply earlier for designation, thus reducing the occurrence of such "blind" competition.

According to 21 C.F.R. § 20.61, trade secret and confidential commercial or financial information must be kept secret.¹⁵⁵ However, after orphan designation, the FDA will publish the name and address of the manufacturer, the generic and trade names of the drug, the rare disease or condition for which orphan designation was granted, and the proposed indication for use of the drug.¹⁵⁶ Since the FDA publishes this information after designation, it is not clear why it will not publish this limited information before designation.¹⁵⁷ The FDA should publish limited information about applications for designation before acting upon them. Failing that, the agency should act on these applications as soon as possible, so that a notice of the designation can be published promptly.

The absence of regulations in the eight years since the Act was passed

155. It is impossible to market a drug whose identity is a trade secret because detailed labeling information must accompany the drug when it is sold. See 21 C.F.R. § 201 (1990). Nevertheless, protection of a drug's identity prior to its approval may be important to a pharmaceutical company because it may wish to continue research into variants of the drug if approval of the original drug is denied. The fact that the company is pursuing approval of an orphan drug may also be valuable financial or commercial information, but companies often disclose this anyway.

156. 56 Fed. Reg. 3338, 3350 (to be codified at 21 C.F.R. § 316.28).

157. Designation usually occurs prior to approval. A request for designation must be submitted before the application for marketing approval is submitted. *Id.* at 3349 (to be codified at 21 C.F.R. § 316.23).

had been another cause of uncertainty. Companies could not easily foresee whether their applications would be approved or rejected. Even after approval, the FDA could interfere with their market exclusivity rights by approving a competitor's variant of the same drug. Now that the agency has finally proposed regulations, one source of uncertainty will be reduced.

Legislative controversy about the Act also "undermine[s] the economic certainty necessary to reasonably assure maintenance of [market] incentives."¹⁵⁸ The idea of altering market exclusivity has been discussed for three years, and "[t]he mere pendency of these proposals was seen by some as a reason to avoid making the necessary commitment to undertake research in this area."¹⁵⁹ Passing the 1990 Amendments would have finally settled the issue of altering the market exclusivity provision. At present, however, this issue remains unresolved.

B. The Weakness of the Tax Credit Incentive

The tax credit is limited in its scope. It only covers human clinical testing, not pre-clinical testing.¹⁶⁰ The credit is neither refundable nor recapturable,¹⁶¹ so a company only benefits if it has sufficient income in that particular year so that the tax it owes is more than the minimum tax.¹⁶² The technical requirement of "carrying on business" to qualify for the credit may exclude companies which do not yet sell drugs, such as start-up companies, research partnerships, nonprofit organizations, or university researchers.¹⁶³ This is especially disadvantageous for biotechnology companies, which frequently make very little profit and often do not market products until many years after start-up.¹⁶⁴

"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

158. 136 CONG. REC. H11,932 (daily ed. Oct. 23, 1990) (statement of Rep. Richardson).

159. *Id.* The President of the Industrial Biotechnology Association reports that the continuing uncertainty about whether the Act will be amended is making it difficult to fix future plans and raise capital. CHEMICAL WK., Jan. 2, 1991, at 26.

160. 26 U.S.C.S. § 28(b) (Law Co-op. 1990).

161. If a tax credit is refundable, the credit in excess of a company's tax liabilities is refunded by the government. If a tax credit is recapturable, it can be carried over to a prior or subsequent year in which the company has more income and therefore more tax liabilities. Richardson, *supra* note 78, at 193-94.

162. 26 U.S.C.S. § 28(d)(2) (Law Co-op. 1990).

163. Richardson, *supra* note 78, at 180-86.

164. *Id.* at 203.

continues to act as a barrier to development of true orphan drugs."¹⁶⁵ The National Commission on Orphan Diseases ("Commission") has also recommended that the tax credit be expanded to cover all developmental activities.¹⁶⁶ Legislation should be passed that will expand the scope of research and development activities qualifying for the tax credit, and the credit should be made at least recapturable, if not refundable.¹⁶⁷

C. The Long and Arduous Drug Approval Process

The FDA has been heavily criticized recently for its slow drug approval process in general. The Commission found widespread sentiment among researchers that FDA personnel were insensitive to the special circumstances of clinical testing for small total patient populations,¹⁶⁸ despite FDA's assurances that the approval process is more flexible for orphan drugs.¹⁶⁹ The FDA should make special efforts in orphan drug cases to speed approval; under normal circumstances, the FDA is often months behind the 180-day requirement for review of NDAs.¹⁷⁰

D. The Possibility of Liability

Clinical testing in a smaller patient population necessarily means that some problems will not appear until after the drug has been approved and has been in use for some time. The tolerable level of risks may also be somewhat higher for orphan drugs, where the benefits of some treatment versus no treatment at all are clearly substantial. The Commission has reported that fears of liability have discouraged some companies

165. 136 CONG. REC. H6194 (daily ed. July 31, 1990) (statement of Rep. Stark).

166. COMMISSION REP., *supra* note 67, at 58.

167. Some members of Congress have considered these issues. For example, S. 2577, 101st Cong., 2d Sess. (1990), contained a provision which would expand the tax credit to cover pre-clinical testing. H.R. 5421, 101st Cong., 2d Sess. (1990), had a similar provision, and would also have made the tax credit recapturable. Although expanding tax credits is likely to be unpopular in the current budgetary climate, fostering development of new orphan drugs in this way may be less costly than spending large amounts through Medicare, Medicaid, and Social Security on the health care and disability payments that rare disease sufferers require. "As just one example, patients with Parkinson's disease who can slow their disease progression with the orphan drug selegiline may save the public \$10 million per week by delaying the initiation of disability payments and by providing tax revenues while they continue to work." Ashbury, *supra* note 71, at 897 (citing Lewin, *Big First Scored with Nerve Diseases*, 245 SCI. 467 (1989)).

168. COMMISSION REP., *supra* note 67, at 62.

169. "FDA has a longstanding policy of approving NDA's on the basis of studies with relatively few patients when the disease in question is rare and the benefit-risk considerations are clearly favorable." H.R. REP. NO. 840(I), *supra* note 3, at 3583.

170. COMMISSION REP., *supra* note 67, at 62.

from developing orphan drugs, and that lack of liability insurance has delayed the availability of some drugs.¹⁷¹ Creative solutions to this problem should be developed, such as government-supported insurance pools, legislative tort reform, or cooperative private efforts.¹⁷²

E. The Need for Basic Scientific Research

Now that the Act has successfully addressed some of the barriers to development of known orphan drugs, some thought should be given to the basic scientific research needed for discovery of new orphan drugs. The Commission recommended the following steps: (1) expanding funding for basic research on orphan drugs; (2) encouraging inter-organizational cooperation between researchers, physicians, rare disease sufferers, and rare disease advocacy organizations so that serendipitous discoveries can be exploited quickly; and (3) expediting technology transfer from federal research laboratories to commercial manufacturers.¹⁷³

CONCLUSION

The Orphan Drug Act has been undisputedly successful in encouraging the development and marketing of new orphan drugs, and its prospects for continued success are excellent. A few companies have taken advantage of loopholes in the Act to circumvent the spirit, if not the letter, of the Act. These instances are few in number, however, and may be avoided by fine-tuning the Act with well-balanced legislation that does not weaken market incentives for truly deserving orphan drugs, like that proposed in the vetoed 1990 Amendments, and by implementing and refining the proposed regulations. The potential for abuse notwithstanding, the incentives should be expanded to provide drugs for those rare diseases that are still without treatment. The tax credit provision should be broadened to provide more of an incentive. Issues that affect all drugs, such as the prolonged approval process and the specter of liability, should be addressed to promote increased production. Finally, basic research into rare diseases and discoveries of new orphan drugs should be encouraged so that the Act's incentives for development will continue to be effective.

171. *Id.* at 60.

172. *Id.*

173. *Id.* at xv-xvii.

