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Citations:

Bluebook 21st ed.

Gary A. Pulsinelli, Orphan Drug Act: What's Right with It, The , 15 Santa CLARA COMPUTER & HIGH TECH. L. J. 299 (1999).

ALWD 7th ed.

Gary A. Pulsinelli, Orphan Drug Act: What's Right with It, The , 15 Santa Clara Computer & High Tech. L. J. 299 (1999).

APA 7th ed.

Pulsinelli, G. A. (1999). Orphan drug act: what's right with it, the Santa Clara Computer and High-Technology Law Journal 15(2), 299-346.

Chicago 17th ed.

Gary A. Pulsinelli, "Orphan Drug Act: What's Right with It, The ," Santa Clara Computer and High-Technology Law Journal 15, no. 2 (1999): 299-346

McGill Guide 9th ed.

Gary A. Pulsinelli, "Orphan Drug Act: What's Right with It, The " (1999) 15:2 Santa Clara Computer & High Tech L J 299.

AGLC 4th ed.

Gary A. Pulsinelli, 'Orphan Drug Act: What's Right with It, The ' (1999) 15(2) Santa Clara Computer and High-Technology Law Journal 299

MLA 9th ed.

Pulsinelli, Gary A. "Orphan Drug Act: What's Right with It, The ." Santa Clara Computer and High-Technology Law Journal , vol. 15, no. 2, 1999, pp. 299-346. HeinOnline.

OSCOLA 4th ed.

Gary A. Pulsinelli, 'Orphan Drug Act: What's Right with It, The ' (1999) 15 Santa Clara Computer & High Tech L J 299

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THE ORPHAN DRUG ACT: WHAT'S RIGHT WITH IT*

Gary A. Pulsinelli†

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I. INTRODUCTION

In the quest for profits, the pharmaceutical industry is one of the leaders in the United States economy. As a consequence of the high profits available, patients benefit from the availability of an ever increasing array of drugs to treat the illnesses and injuries that affect everyone.¹ However, developing and manufacturing drugs are not always profitable for drug companies where the drugs will treat diseases that do not affect many people.² The drugs that treat rare

1. See H.R. REP. NO. 97-840, pt. 1, at 6 (1982), *reprinted in* 1982 U.S.C.C.A.N. 3577, 3578 [hereinafter ORPHAN DRUG ACT REPORT] (report on P.L. 97-414 Orphan Drug Act).

2. See *id.*

diseases have come to be known as "orphan drugs,"³ a reference to the unwillingness of drug companies to "adopt" these drugs and take them through the lengthy and expensive Food and Drug Administration (FDA) approval process that is required before they can be sold in the U.S.⁴ Before 1983, the development of these drugs was left to the benevolence of the drug companies, who would occasionally develop them as a public service.⁵

In 1983, however, Congress passed the Orphan Drug Act.⁶ The Act was designed to encourage the development of orphan drugs through a series of economic incentives and special assistance with the drug approval process. The Act has been extremely successful, leading to enormous increases in the number of drugs that are available to treat rare diseases. In the decade preceding the passage of the Act, only ten orphan drugs were approved and developed without substantial federal support;⁷ in the fourteen years since, that number has increased to 144.⁸ However, like any legislation, the Act also has

3. *Id.* Technically, the proper term is the more general "orphan product," which can refer to a drug, an antibiotic, or a biological product; these three categories receive an approval, a certification, or a license, respectively. See 21 U.S.C. § 360bb(a)(1) (1994). For simplicity, this Article uses "orphan drug" and "approval" throughout; the term is to be taken to mean any of the three categories of orphan products.

4. See generally Louis Lasagne, *Who Will Adopt the Orphan Drugs?*, 3 REGULATION 27 (1979); see also CAROLYN H. ASBURY, ORPHAN DRUGS: MEDICAL VERSUS MARKET VALUE (1985). Dr. Asbury's book provides an excellent in-depth discussion of the situation leading up to the passage of the Orphan Drug Act.

5. See Peter S. Arno et al. *Rare Diseases, Drug Development, and AIDS: The Impact of the Orphan Drug Act*, 73 MILBANK Q. 231, 232-33 (1995) (discussing public service drugs).

6. Orphan Drug Act, Pub. L. No. 97-414, 96 Stat. 2049 (1982) (codified as amended at 21 U.S.C. §§ 360aa-360ee (1994), 26 U.S.C. § 45C (Supp. II 1994), 42 U.S.C. § 236 (1994)).

7. See Carolyn H. Asbury, *Evolution and Current Status of the Orphan Drug Act*, 8 INT'L J. TECH. ASSESSMENT HEALTH CARE 573, 576 (1992); Li-Hsien Rin-Laures & Diane Janofsky, *Recent Developments Concerning the Orphan Drug Act*, 4 HARV. J.L. & TECH. 269, 270 (1991); see generally Office of Orphan Products Development (visited Mar. 27, 1997) <<http://www.fda.gov/orphan/index.htm>>. This Web site, maintained by the FDA's Office of Orphan Products Development, is an excellent source of information about the Orphan Drug Act.

8. See List of Orphan Designations and Approvals (visited Apr. 12, 1999) <<http://www.fda.gov/orphan/DESIGNAT/list.htm>> (listing all designated and approved orphan drugs under the Act); see Orphan Products Approved for Marketing (visited Apr. 12, 1999) <<http://www.fda.gov/orphan/DESIGNAT/recent.htm>> (listing the approvals in the last 12 months, 24 approvals as of Mar. 27, 1997). At least one company now specializes in marketing orphan products under the Orphan Drug Act. See Orphan Products Company (visited Apr. 12, 1999) <<http://www.orphan.com>> (Web site of Orphan Products Company); see also John Henkel, *Orphan Products: New Hope for People with Rare Disorders*, FDA CONSUMER SPECIAL REPORT ON NEW DRUG DEVELOPMENT IN THE UNITED STATES (1995) available at <<http://www.fda.gov/fdac/special/newdrug/orphan.html>> ("Some companies have even sprung up to develop and market orphan drugs exclusively.").

generated its share of controversy. A few critics have questioned the need for the Act, despite the overwhelming evidence of its success.⁹ However, most of the criticism has centered around a few orphan drugs that are manufactured by a few companies, drugs that are immensely profitable, despite the underlying premise of the Act that orphan drugs would not be profitable at all.¹⁰ These profitable orphans have led to what has become almost an annual event in Congress: attempts to amend the Orphan Drug Act.¹¹ However, to date, none of these amendments has succeeded in changing the basic incentive structure of the Act.¹²

Part II of this article discusses the background and history of the Orphan Drug Act and the provisions that currently comprise it. Part II also examines the regulations that were finally instituted in 1993, almost ten years after the passage of the original Act, and their impact on the Act. Part III analyzes the attempts to amend the Act. Finally, part IV analyzes some of the criticism of the Act and explains why most of this criticism is an overreaction to what has been a relatively small problem. Part IV also discusses the few cases that have addressed the Act and explores other proposed uses of the incentive system of the Act. Part V concludes with the assertion that it is unnecessary — and probably dangerous — to repair an Act that is working so well already.

II. THE ORPHAN DRUG ACT

The Orphan Drug Act was passed in 1982 and went into effect in 1983.¹³ It was amended in 1984,¹⁴ 1985,¹⁵ and 1988.¹⁶ Congress has made various other attempts to amend the Act (the closest to success

9. See, e.g., Arno et al., *supra* note 5, at 245 (questioning the need for high returns in the pharmaceutical industry).

10. See, e.g., Arno et al., *supra* note 5, at 232; John J. Flynn, *The Orphan Drug Act: An Unconstitutional Exercise of the Patent Power*, 1992 UTAH L. REV. 389 (1992); Rin-Laures & Janofsky, *supra* note 7, at 269, 293, 297.

11. See, e.g., S. 2576, 101st Cong. (1990) and H.R. 4638, 101st Cong. (1990) (Orphan Drug Amendments of 1990); S. 1981, 103rd Cong. (1994) and H.R. 4160, 103rd Cong. (1994) (Orphan Drug Act Amendments of 1994).

12. The Orphan Drug Amendments of 1990 did pass both houses of Congress, but they were pocket vetoed by President Bush. See 137 CONG. REC. H73 (daily ed. Jan. 3, 1991) (H.R. 4638—Memorandum of Disapproval).

13. The Orphan Drug Act, Pub. L. No. 97-414, 96 Stat. 2049 (1982) (codified as amended at 21 U.S.C. §§ 360aa-360ee (1994), 26 U.S.C. § 45C (Supp. II 1994), 42 U.S.C. § 236 (1994)).

14. Health Promotion and Disease Prevention Amendments of 1984, Pub. L. No. 98-551, 98 Stat. 2815 (1984).

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

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

in 1990)¹⁷; the provisions of these failed Amendments are discussed in part III, *infra*. The FDA finally formalized the Regulations under the Act in 1993.¹⁸ Part II.A provides the background of the problems that cause some drugs to become orphans. Part II.B traces the chronology of the various parts of the Act and the Regulations. Part II.C then discusses the specific provisions of the current Act, while part II.D discusses the Regulations.

A. Background

The root of the orphan drug problem lies in the complex and costly FDA drug approval process. Before the 1960s, drug approval was a relatively simple process, requiring only a demonstration that the compound in question was safe and that it was labeled properly.¹⁹ However, in 1962 Congress amended the Food, Drug, and Cosmetic Act to require a showing of efficacy in addition to safety.²⁰ This led to the creation of the modern drug approval process.

The FDA requires many difficult steps in a drug's long journey from the laboratory to the pharmacy. Once a drug with a potentially therapeutic effect has been found, it must first be tested in animals for both safety and efficacy.²¹ This process is very time-consuming. When the drug has passed the animal hurdle, it must then go through three levels of testing in humans to demonstrate again its safety and efficacy. In many cases, post-marketing testing is required as well.²² After completing all of these hurdles, drug companies must then compile all of the information and submit it to the FDA to obtain approval. This compilation process is anything but easy; drug approval applications can be tens of thousands of pages long.²³ Over time, the FDA has become more and more demanding, requiring additional information at each of these levels. All of this is after the enormous investment of money and effort that is required even to

17. See S. 2576, 101st Cong. (1990) and H.R. 4638, 101st Cong. (1990) (Orphan Drug Amendments of 1990).

18. 21 C.F.R. pt. 316 (1998).

19. See LISA RUBY BASARA & MICHAEL MONTAGNE, *SEARCHING FOR MAGIC BULLETS* 78 (1994).

20. See Drug Amendments of 1962, Pub. L. No. 87-781, 76 Stat. 780 (1962). For a history of the drug approval process in the U.S., see ASBURY, *supra* note 4, at 7-45. See also BASARA & MONTAGNE, *supra* note 19, at 77-108.

21. See BASARA & MONTAGNE, *supra* note 19, at 85-98.

22. See BASARA & MONTAGNE, *supra* note 19, at 97-98; Veronica Henry, *Problems with Pharmaceutical Regulation in the United States*, 14 J. LEGAL MED. 617, 620-22 (1993); see generally ASBURY, *supra* note 4, at 7-45.

23. See Henry, *supra* note 22, at 622.

identify potential drug candidates. Thus, drug development is a very expensive and time-consuming process. Estimates vary widely, but in general it costs on average over \$300 million and takes more than ten years to bring a drug to market.²⁴

For most drugs that are designed to treat conditions affecting many people, these costs can be recovered in the sales of the drug. The profitability of such drugs is enhanced since almost all of them are patented, which gives the maker exclusive marketing rights. Large markets and patents are sufficient incentives for the development of most drugs.²⁵

Drugs for rare conditions that affect very few people in the United States are different. The market for these drugs may be so small that the manufacturer has no expectation of recovering the costs of developing the drug.²⁶ Further complicating the development process is the fact that these drugs affect so few people that designing effective clinical trial protocols is particularly difficult (although this sometimes makes the drugs less expensive to develop, as the FDA often allows manufacturers to use fewer subjects in trials of drugs for rare diseases). The cost-recovery problem is exacerbated by the fact that many of these drugs are already known to have the desired effect on the rare disease, and hence are not eligible for either product or use patents.²⁷ Thus, in the past, drug companies were reluctant to develop these drugs, since without patent protection they were vulnerable to certain types of competition. After a drug company made an investment in the testing required to get approval of a drug, copycat drug makers who did not incur the testing and approval costs could easily underprice them. Without the assurance of a protected market, especially when the market itself was so small, the only reason to develop these drugs was as a public service. The drugs that were

24. See, e.g., George Anders, *Vital Statistic: Disputed Cost of Creating a Drug*, WALL ST. J., Nov. 9, 1993, at B1 (presenting a range of \$129 million after taxes to \$500 million before taxes; Office of Technology Assessment reports \$359 million before taxes); Henry, *supra* note 22, at 617 (\$231 million).

25. See generally Peter Temin, *Technology, Regulation and Market Structure in the Modern Pharmaceutical Industry*, 10 BELL J. ECON. 429, 435-41 (1979).

26. See Marlene E. Haffner & John V. Kelsey, *Evaluation of Orphan Products by the U.S. Food and Drug Administration*, 8 INT'L J. TECH. ASSESSMENT HEALTH CARE 647, 647-648 (1992). Dr. Haffner is the Head of the FDA's Office of Orphan Products Development.

27. See Asbury, *supra* note 7, at 575 (noting that some orphan drugs are not patentable because they are "shelf chemicals, natural substances, products whose patents had already expired, [or] 'known' through publication"). Researchers (often in universities) discovered the effect of many orphan drugs on their respective diseases, but without the Act, drug companies did not find these drugs worth developing or patenting. The failure to file a patent application before publication resulted in the eventual loss of potential patent rights.

already known to be effective for treating rare diseases were called "orphan drugs" because drug companies were unwilling to adopt them and take them through the FDA's drug approval process.²⁸

While the individual diseases may be rare, enough of these rare diseases exist that in the aggregate that they affect between ten and twenty million people in the U.S.²⁹ Thus, in the early 1980s, Congress began to take an interest in resolving the orphan drug problem.³⁰ This Congressional interest culminated in the Orphan Drug Act of 1983.³¹ One of the major driving forces behind the legislation was the National Organization for Rare Diseases (NORD), led by its chairperson, Abbey Meyers.³² However, the event that finally catalyzed the passage of the Act was the public outcry following the broadcast of an episode of the television show *Quincy, M.E.* in March 1981.³³ This episode dealt with a boy with Tourette's Syndrome, a classic orphan disease. Such was the power of the episode (and the public sentiment that followed it) that Congress passed the Act by an overwhelming majority.

B. Chronology

1. The 1983 Act

Congressional hearings and proposals on orphan drugs began as early as 1980, and the original Orphan Drug Act was finally passed in December 1982.³⁴ The Orphan Drug Act of 1983 laid out the basic elements of the Act that persist today.

The Act first defined an orphan drug as one that was useful for a

28. See Asbury, *supra* note 7, at 575.

29. See Marlene E. Haffner, *Orphan Products: Origins, Progress, and Prospects*, 31 ANN. REV. PHARMACOLOGY & TOXICOLOGY 603, 603 (1991) (quoting the 1989 Report of the National Commission on Orphan Diseases).

30. See Asbury, *supra* note 7, at 576 (discussing Congressional hearings on H.R. 7089 in 1980).

31. Pub. L. No. 97-414, 96 Stat. 2049 (1982) (codified as amended at 21 U.S.C. §§ 360aa-360ee (1994), 26 U.S.C. § 45C (Supp. II 1994), 42 U.S.C. § 236 (1994)).

32. See Abbey S. Meyers, *The Impact of Orphan Drug Regulation on Patients and Availability*, 47 FOOD DRUG & COSMETIC L.J. 9, 9 (1992). For more information on NORD and the amazing work it does for people with rare diseases, see <<http://www.rarediseases.org>>.

33. See ASBURY, *supra* note 4, at 111-12, 124-26, 166. See also BASARA & MONTAGNE, *supra* note 19, at 133-34 (pointing out that many other people were also deeply involved in persuading Congress to pass the Orphan Drug Act). The star of *Quincy*, Jack Klugman, actually testified at the House of Representatives' Hearings on the Orphan Drug Act. For a fascinating discussion of the crucial role played by Klugman and *Quincy*.

34. Orphan Drug Act, Pub. L. No. 97-414, 96 Stat. 2049 (1982) (codified as amended at 21 U.S.C. §§ 360aa-360ee (1994)).

condition that was "rare in the United States."

[T]he term "rare disease or condition" means any 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 in the United States of such drug.³⁵

Congress intentionally left this definition vague, giving instructions for the FDA to define orphan drugs more precisely. Congress gave the FDA guidance in the Findings that accompanied the Act:

The Findings state [sic] that when a disease or condition occurs infrequently, so that the sponsor of a drug has no reasonable expectation of its sales generating sufficient revenues to offset the costs of development, the disease or condition is probably "rare" enough to discourage development. This statement is not intended to establish a test of the "commercial value" of a drug, but rather to direct FDA to the incidence of the disease and whether the expected low use of a drug is the determining factor in whether drug development will occur.³⁶

Thus, under the original version of the Act, an orphan drug was defined as one for which there was "no reasonable expectation that the cost of developing . . . will be recovered from sales in the United States of such drug."³⁷ To qualify for the market exclusivity incentive, the drug also had to be unpatented and unpatentable, since a patent was thought to give sufficient protection without the need for the incentives of the Act.³⁸ A drug that met this definition was to be given "designation" as an orphan drug, which entitled the manufacturer to take advantage of the Act's incentives.³⁹ Any number of sponsors could obtain designation for the same drug for the

35. Orphan Drug Act, Pub. L. No. 97-414, § 526(a)(2), 96 Stat. 2049 (1982) (codified as amended at 21 U.S.C. § 360bb(a)(2) (1994)).

36. ORPHAN DRUG ACT REPORT, *supra* note 1, at 5.

37. Orphan Drug Act, Pub. L. No. 97-414, § 526(a)(2), 96 Stat. 2049 (1982) (codified as amended at 21 U.S.C. § 360bb(a)(2) (1994)).

38. See Orphan Drug Act, Pub. L. No. 97-414, § 527(a), 96 Stat. 2049 (1982); see generally Sheila R. Shulman et al., *Implementation of the Orphan Drug Act: 1983-1991*, 47 FOOD & DRUG L.J. 363, 364 (1992); ORPHAN DRUG ACT REPORT, *supra* note 1, at 6-7.

39. See Orphan Drug Act, Pub. L. No. 97-414, § 526, 96 Stat. 2049 (1982) (codified as amended at 21 U.S.C. § 360bb (1994)). Currently, approximately 660 drugs have been designated under the Act. See *OOPD Frequently Asked Questions* (visited Apr. 12, 1999) <<http://www.fda.gov/orphan/faq/index.htm>>. See *List of Orphan Designations and Approvals* (visited Apr. 12, 1999) <<http://www.fda.gov/orphan/DESIGNAT/list.htm>> (listing all designated and approved orphan drugs under the Act).

same indication. However, only the first one to receive FDA marketing approval, gained by successfully completing clinical trials, was entitled to receive market exclusivity. Any particular drug could qualify for exclusivity for treating any number of different diseases or indications.⁴⁰ Additionally, any particular disease or indication could have any number of drugs for treating it qualify for exclusivity. The sole limitation was that only one manufacturer could obtain exclusivity for any given drug for any given indication, since otherwise "exclusivity" would be meaningless.⁴¹

The details of the incentives are discussed in part II.C, *infra*. Briefly, the Act provided: (1) assistance from the FDA in designing clinical trials for orphan drugs; (2) seven years of market exclusivity for orphan drugs; (3) open clinical trial protocols to increase availability of experimental orphan drugs; (4) the creation of an Orphan Products Board to coordinate the government's orphan drug programs; (5) tax credits for clinical trials of orphan drugs; and (6) grant funds for orphan drug research and clinical trials.⁴²

2. The 1984 Amendments

The response to the 1983 Orphan Drug Act was underwhelming.⁴³ Drug manufacturers were reluctant to incur the costs of compiling the production-cost information that was needed to demonstrate the lack of commercial feasibility, and they were even more reluctant to share this sensitive information with the FDA. In response, Congress passed the 1984 Amendments,⁴⁴ establishing a bright-line rule which defined an orphan drug as one for a disease that affected fewer than 200,000 people in the U.S. Congress also maintained the previous definition for drugs that had costs which could not be recovered by sales. This test was to be used for drugs that affected more than 200,000 people. This is the definition currently used in the Orphan Drug Act.⁴⁵

40. See Shulman et al., *supra* note 38, at 370.

41. See Shulman et al., *supra* note 38, at 370-71 (giving specific examples of both of these situations).

42. See 21 U.S.C. §§ 360aa-360ee (1994), 26 U.S.C. § 45C (Supp. II 1994), 42 U.S.C. § 236 (1994).

43. See Stephan E. Lawton, *Controversy Under the Orphan Drug Act: Is Resolution on the Way?*, 46 FOOD DRUG & COSMETIC L.J. 327, 329 (quoting Edward Brandt, Assistant Secretary of Health, Department of Health and Human Services); see also Shulman et al., *supra* note 38, at 365; Asbury, *supra* note 7, at 578.

44. Health Promotion and Disease Prevention Amendments of 1984, Pub. L. No. 98-551, 98 Stat. 2815 (1984).

45. See 21 U.S.C. § 360bb(a)(2) (1994).

3. The 1985 Amendments

The most important aspects of the 1985 Amendments to the Orphan Drug Act addressed the unpatentability requirement.⁴⁶ The requirement that the drug be unpatented and unpatentable created problems in several types of situations.⁴⁷ First, some drugs were patented, but their patent terms were set to expire in less than seven years, the market exclusivity period under the Act. Under the existing Act, such drugs did not receive the full seven years of market exclusivity, one of the main incentives under the Act. In some cases, the FDA delayed approval until the patent term expired, but this was a poor solution because the purpose of the Act was to get orphan drugs to patients who needed them as quickly as possible; the delay was particularly problematic when the remaining patent term was several years. Second, deciding whether or not a drug was "patentable" could be a very difficult and time-consuming endeavor,⁴⁸ even with the assistance of the Patent and Trademark Office.⁴⁹ This situation again led to excessive and unnecessary delays in the approval of orphan drugs. Congress elected to address this problem by simply removing the requirement that the drug be unpatented and unpatentable.⁵⁰

The 1985 Amendments also made some other minor changes to the Orphan Drug Act. The Act was expanded to include antibiotics (the original Act covered only traditional pharmaceuticals and biologics such as vaccine sera), necessitating minor wording changes throughout the Act. The Amendments also expanded the availability of research grants to cover all "qualified testing" rather than just "qualified clinical testing" and reauthorized these grants for three more years.

4. The 1988 Amendments

The 1988 Amendments⁵¹ were less significant than the previous Amendments. Congress was concerned with perceived problems with the Orphan Drug Act, and some Congresspersons called for drastic

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

47. See H.R. REP. NO. 99-153, at 3 (1985), *reprinted in* 1985 U.S.C.C.A.N. 301, 302-03 (report on P.L. 99-91 Orphan Drug Amendments of 1985).

48. See Arno et al., *supra* note 5, at 234.

49. See Memorandum of Understanding with the United States Patent and Trademark Office, 49 Fed. Reg. 13589 (1984) (PTO to assist FDA in determining patentability of orphan drugs).

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

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

reform.⁵² However, Congress decided to reauthorize the Act before some of its provisions (especially the grant appropriations) expired. Congress at that time chose to defer major changes. Most of the 1988 changes simply repaired minor errors. A 1993 Amendment similarly corrected some very minor technical errors.⁵³

The 1988 Amendments did make two substantive changes. First, the Act was amended to require that the sponsor file the request for orphan drug designation before submitting an application for drug marketing approval.⁵⁴ Second, a new provision required that orphan drug manufacturers notify the FDA at least one year before discontinuing production of an approved orphan drug product.⁵⁵ This time lag gives the FDA time to find another manufacturer for the drug.⁵⁶ Holders of orphan drug designations for drugs that are not yet approved for sale were also required to notify the FDA when they were no longer actively pursuing FDA approval.⁵⁷

5. The 1993 Regulations

In January 1991, the FDA finally proposed the regulations under which it would administer the Orphan Drug Act.⁵⁸ These regulations established the process for obtaining orphan drug designation and explained what information would be required under both parts of the orphan drug definition (the "less than 200,000 affected" and "no reasonable expectation of cost recovery" prongs). The regulations resolved the long-standing problem of under what circumstances two drugs would be considered "different" for the purposes of market exclusivity. They also made an attempt to define when different medical conditions represent different drug markets. After a period of comment, these Regulations went into effect, with only slight modifications, in January 1993 — almost ten years after the original passage of the Orphan Drug Act.⁵⁹

52. See Cynthia A. Thomas, *Re-Assessing the Orphan Drug Act*, 23 COLUM. J.L. & SOC. PROBS. 413, 435-36 (1990); Rin-Laures & Janofsky, *supra* note 7, at 275-76.

53. See Nutrition Labeling and Education Act Amendments of 1993, Pub. L. No. 103-80, 107 Stat. 773 (1993).

54. See Orphan Drug Amendments of 1988, Pub. L. No. 100-290, 102 Stat. 90 (1988) (codified as amended at 21 U.S.C. § 360bb(a)(1) (1994)).

55. See *id.* § 360bb(b)(1) (1994).

56. See Rin-Laures & Janofsky, *supra* note 7, at 276.

57. See Orphan Drug Amendments of 1988, Pub. L. No. 100-290, 102 Stat. 90 (1988) (codified as amended at 21 U.S.C. § 360bb(b)(2) (1994)).

58. 56 Fed. Reg. 3338 (1991) (to be codified at 21 C.F.R. pt. 316) (proposed Jan. 29, 1991).

59. Orphan Drugs, 57 Fed. Reg. 62076 (1992) (codified at 21 C.F.R. pt. 316).

C. Orphan Drug Act Provisions

The Orphan Drug Act provides manufacturers with six main areas of assistance in developing orphan drugs. Three of these are direct economic incentives, while the other three primarily facilitate the development process.

1. Protocol Assistance

The first incentive provided in the Orphan Drug Act was assistance with investigations of orphan drugs.⁶⁰ As discussed in part II.A, *supra*, the FDA approval process is very complex and costly. It is often made even more costly because drug manufacturers do not always know in advance the data requirements of the FDA for granting approval. To reduce this problem, the Act provides for orphan drug sponsors to receive assistance directly from the FDA on exactly what tests and experiments the sponsors need to complete in order to secure drug marketing approval. This assistance is especially helpful with orphan drugs, since the diseases that these drugs treat affect so few people that drug companies face particular difficulties in designing effective clinical trials.⁶¹

2. Marketing Exclusivity

The second incentive is the most significant incentive, and also the most controversial. The Orphan Drug Act provides for a seven-year period of market exclusivity for orphan drugs.⁶² This provision takes advantage of the FDA's role in approving pharmaceutical products.⁶³ Normally, the only way to protect the market for a product or treatment is by obtaining a patent. However, another form of protection is available for drugs. Since the FDA must approve all drugs before they can be sold in the U.S., the FDA can protect the market for a drug simply by refusing to approve the applications of competing drugs. Congress has taken advantage of this special form of market protection in the Orphan Drug Act. The Act provides that the FDA cannot approve a marketing application for the same orphan drug that treats the same orphan condition for seven years from the date of the approval of the first orphan drug application. The effect of this provision is to confer a monopoly of seven years to the first sponsor with an approved application.

60. See 21 U.S.C. § 360aa (1994).

61. See H.R. REP. NO. 97-840, pt. 1, at 7 (1982), *reprinted in* 1982 U.S.C.C.A.N. 3577.

62. See 21 U.S.C. § 360cc (1994).

63. See *supra* Part II.A.

The Act provides for two exceptions to this rule. The first is that if the FDA finds that the sponsor cannot produce enough of the drug to meet the demand for it, the exclusivity is revoked.⁶⁴ This provision is a required safety valve, although it has not yet been invoked. Second, the holder of the marketing exclusion can voluntarily consent in writing to the approval of another application.⁶⁵ This provision has been used and it provides an important mechanism whereby drug manufacturers can arrange their business dealings with each other.

This provision was originally intended to compensate for a lack of patent protection.⁶⁶ Consequently, it was written to apply only to drugs that could not be or were no longer patented. However, this proved to be unworkable, and the 1985 Amendments removed this requirement.

The market exclusivity provision has proven to be quite controversial. For the most part, it has been very successful in protecting orphan drugs and getting them to market. However, in a few instances it has protected drugs that are immensely profitable, drugs that presumably would have been developed even without the incentives of the Act. These few exceptional drugs have been the source of considerable concern to many people. Congresspersons, activists, patients, and commentators have all demanded reform of the Act to prevent this situation from recurring in the future.⁶⁷ To date, these reform attempts have all been unsuccessful. This issue will be discussed in much more detail in parts III and IV, *infra*. However, these few drugs are exceptional and the problem temporary. The situation does not warrant the attention paid to it. Like most legislation, the Act has had some unforeseen negative consequences. Unlike most legislation, however, the Act has also been extremely successful in what it attempts to accomplish — getting orphan drugs to market. As such, it is dangerous to tinker with the Act and risk destroying its effectiveness over a few cases of "misuse."

3. Open Protocols

The Orphan Drug Act also provides a means for more easily getting the drugs to the patients who need them.⁶⁸ Manufacturers are

64. See 21 U.S.C. § 360cc(b)(1) (1994).

65. See 21 U.S.C. § 360cc(b)(2) (1994).

66. See *supra* Part II.B.

67. See, e.g., Arno et al., *supra* note 5; Meyers, *supra* note 32; 137 CONG. REC. E2435-37 (daily ed. June 27, 1991) (article critical of the Orphan Drug Act inserted into the record by Rep. Gerry Studds).

68. See 21 U.S.C. § 360dd (1994).

encouraged to use open protocols for their clinical trials.⁶⁹ Open protocols allow the manufacturer to make the orphan drug available to patients who are not participating in the clinical trials while the trials are still ongoing. This provision is not so much an incentive to the manufacturers as it is a boon to patients. However, it gives the manufacturers an opportunity to recoup some costs by selling drugs to patients before receiving full approval, and it may also help the companies generate more test data.⁷⁰

4. Orphan Products Board

Another way the Orphan Drug Act helped drug manufacturers is by establishing an Orphan Products Board in the Department of Health and Human Services (DHHS), the body with authority over the FDA.⁷¹ The Board is charged with coordinating the various government agencies that are involved in the development of orphan drugs and keeping all interested parties informed. Many of the expected functions of this Board, such as the administration of the orphan drug grant program, have actually fallen to the FDA's Office of Orphan Product Development.⁷²

5. Tax Credits

The second big financial incentive provided by the Orphan Drug Act is a tax credit for "qualified clinical testing expenses."⁷³ The tax credit is for fifty percent of the amounts spent conducting clinical trials. The original Senate bill called for a ninety percent credit, while the House bill called for no tax credit.⁷⁴ The two bodies chose fifty percent as the compromise number. The tax credit is not refundable and it could not be carried forward or backward. The tax is subject to a periodic renewal; this provision expired on May 31, 1997.⁷⁵

6. Grants

The final incentive provided by the Orphan Drug Act is grants to

69. See Haffner, *supra* note 29, at 608-09.

70. See Henry, *supra* note 22, at 624 (discussing Treatment INDs).

71. See 42 U.S.C. § 236 (1994).

72. See *Welcome to the Office of Orphan Products Development (OOPD)* (visited Apr. 12, 1999) <<http://www.fda.gov/orphan/index.htm>>.

73. 26 U.S.C. § 45C (Supp. II 1994).

74. See Donna Brown Grossman, *The Orphan Drug Act: Adoption or Foster Care?*, 39 *FOOD DRUG & COSMETIC L.J.* 128, 138-41 (1984).

75. See 26 U.S.C. § 45C(e)(2) (Supp. II 1994).

defray the costs of "qualified testing."⁷⁶ This originally only included clinical trials in humans, but the 1988 Amendments expanded the definition to cover all testing after a drug is designated as an orphan drug.⁷⁷ The grants are subject to periodic renewal, and the amount available has increased with time.

D. Regulation Provisions

A long time elapsed between the passage of the Orphan Drug Act and the FDA's promulgation of Regulations for implementing it, as required by the Act.⁷⁸ Commentators frequently noted this delinquency.⁷⁹ In the FDA's defense, Congress amended the Act three times during this delay, and threatened to amend it on several other occasions. When the Regulations were finally enacted, they resolved several troubling issues.⁸⁰

1. Information Disclosure

The Regulations formalized the procedure for obtaining orphan drug designation.⁸¹ The Regulations now specify the format for an orphan drug designation request and the information required.⁸² They also for the first time set forth the data required to demonstrate that a drug is unlikely to be profitable even though the disease it treats affects more than 200,000 people⁸³ (although, since no drug company has ever attempted to obtain designation under this provision, this omission was not a large problem). The Regulations also define the conditions for the approval, refusal, and revocation of orphan drug designation.⁸⁴ Importantly, the Regulations provide sanctions for the

76. 21 U.S.C. § 360ee (1994).

77. See Orphan Drug Amendments of 1988, Pub. L. No. 100-290, 102 Stat. 90. The 1988 amendments also expanded the grants program to cover orphan medical devices and medical foods; however, devices and foods are not eligible for the other incentives of the Act, particularly the market exclusivity. See *id.*

78. See 21 U.S.C. § 360bb(d) (1994).

79. See, e.g., Lawton, *supra* note 43, at 332; Rin-Laures & Janofsky, *supra* note 7, at 277.

80. The FDA lacked the power to rectify all the problems of the Act, despite the demands of some commentators. The FDA was, of course, limited by the text of the statute. See, e.g., Arno et al., *supra* note 5, at 246; Meyers, *supra* note 32.

81. Before the issuance of the Regulations, the FDA administered the Orphan Drug Act under a set of interim guidelines. See Implementation of the Orphan Drug Act of 1983, 48 Fed. Reg. 40784 (1983) (proposed Sept. 9, 1983) (notice of availability of interim procedures).

82. See 21 C.F.R. § 316.10 (1998).

83. See 21 C.F.R. § 316.21(c) (1998).

84. See 21 C.F.R. §§ 316.24, 316.25, 316.29 (1998).

misstatements of fact in any application.⁸⁵ They also elaborate the details for administering the market exclusivity provision⁸⁶ and the open protocol provision.⁸⁷ Finally, the Regulations clarify what information the FDA holds confidential and what information it releases to the public.⁸⁸

2. Same Drug

One of the most troubling problems the FDA faced in administering the Orphan Drug Act was deciding whether two drugs were the "same" for the purposes of market exclusivity. Before the issuance of the Regulations, the FDA decided this question on a case-by-case basis.⁸⁹ Occasionally, the courts had to resolve difficulties.⁹⁰ Proteins and other biologicals presented particular difficulties in this context.⁹¹

The FDA resolved this issue with a series of fairly straightforward definitions and rules. For "small molecule" pharmaceuticals, two drugs are the "same" if they share the same "active moiety," which is defined to be the core molecule of the drug, excluding noncovalent attachments.⁹² However, even if two drugs are the same under these criteria, "if the subsequent drug can be shown to be clinically superior to the first drug, it will not be considered to be the same drug."⁹³ "Clinically superior" is defined to mean: (1) having greater effectiveness (which generally must be demonstrated by a direct comparative clinical trial);⁹⁴ (2) having greater safety in a significant portion of the target population;⁹⁵ or (3) "otherwise mak[ing] a major contribution to patient care."⁹⁶

For "large molecules (macromolecules)," the rules are more

85. See 21 C.F.R. § 316.29(a) (1998).

86. See 21 C.F.R. §§ 316.31, 316.34, 316.36 (1998).

87. See 21 C.F.R. § 316.40 (1998).

88. See 21 C.F.R. §§ 316.50, 316.52 (1998).

89. See Lawton, *supra* note 43, at 332.

90. See *Genentech, Inc. v. Bowen*, 676 F. Supp. 301 (D.D.C. 1987) (discussed *infra* Part IV.D).

91. This same problem also troubles patent attorneys and patent examiners.

92. 21 C.F.R. §§ 316.3(b)(13)(i), 316.3(b)(2) (1998).

93. 21 C.F.R. § 316.3(b)(13)(i) (1998).

94. See 21 C.F.R. § 316.3(b)(3)(i) (1998).

95. See 21 C.F.R. § 316.3(b)(3)(ii) (1998).

96. 21 C.F.R. § 316.3(b)(3)(iii) (1998). The notes accompanying the final Regulations indicate that this includes such things as allowing oral dosing of a drug formerly available only for injection. See 57 FED. REG. 62076 (1992) (to be codified at 21 C.F.R. pt. 3161 (issued Dec. 29, 1992)).

complex, and the Regulations use separate definitions for proteins, polysaccharides, polynucleotides, and "complex partly definable drugs . . . such as . . . live viral vaccines."⁹⁷ Two proteins are the same if they have only minor differences in amino acid sequence. If they differ in ways that may be more important, such as in glycosylation patterns or tertiary structures, they are presumed to be the same unless the second protein demonstrates clinical superiority.⁹⁸ Two polysaccharides are presumed to be the same if they consist of identical repeating units, even if they vary in number or are modified. Again, this presumption can be overcome with a showing of clinical superiority.⁹⁹ Polynucleotides are the same if they have the same sequence and the same sugar backbone (ribose or deoxyribose), subject to a demonstration of clinical superiority.¹⁰⁰ Finally, closely related complex partly definable drugs are considered identical unless the applicant proves the later drug to be clinically superior.¹⁰¹

These definitions should resolve most of the difficulties associated with deciding whether or not two drugs are the same.

3. Disease Subsets

The other big problem addressed by the Regulations is the "salami slicing" problem. "Salami slicing" refers to the practice of artificially dividing one disease into arbitrary subsets, so that these subsets contain fewer than 200,000 afflicted individuals and the drugs for treating them are eligible for orphan drug designation.¹⁰² If a company is successful with this approach, it may acquire multiple approvals for the same drug for treating what are essentially facets of the same disease and obtain market exclusivity for a drug that is not really an orphan. This process abuses the principles of the Act.¹⁰³

97. 21 C.F.R. § 316.3(b)(13)(ii) (1998).

98. See 21 C.F.R. § 316.3(b)(13)(ii)(A) (1998). The wording of the rule seems to suggest that sponsors of protein drugs with minor changes in amino acid sequence will not be given a chance to demonstrate clinical superiority, which may not be the best result.

99. See 21 C.F.R. § 316.3(b)(13)(ii)(B) (1998).

100. See 21 C.F.R. § 316.3(b)(13)(ii)(C) (1998).

101. See 21 C.F.R. § 316.3(b)(13)(ii)(D) (1998).

102. See 57 Fed. Reg. 62076, 62077 (1992) (to be codified at 21 C.F.R. pt. 316) (issued Dec. 29, 1992) (response to comment 12); see also Rin-Laures & Janofsky, *supra* note 7, at 288; Patricia J. Kenney, *The Orphan Drug Act—Is It a Barrier to Innovation? Does It Create Unintended Windfalls?*, 43 FOOD DRUG & COSMETIC L.J. 667, 678 (1988). One of the more striking attempts in this direction was an attempt "to get orphan drug status for a drug to relieve knee pain. Left-knee pain." John Carey & Joan O'C. Hamilton, *These 'Orphans' Don't Need Any Nurturing*, BUS. WEEK July 2, 1990, at 38.

103. See 57 Fed. Reg. 62076, 62077 (1992) (to be codified at 21 C.F.R. pt. 316) (issued Dec. 29, 1992) (response to comment 12); see also Rin-Laures & Janofsky, *supra* note 7, at

The FDA has attempted to prevent this situation on a case-by-case basis wherever possible, although some critics state that the FDA has not been entirely successful.¹⁰⁴ The Regulations codify and clarify the approach the FDA uses in making its determination. If a company attempts to obtain designation for treating a subset of people with a particular disease, the company must present "a demonstration that the subset is medically plausible."¹⁰⁵ This definition has been attacked as vague and ineffective. However, as the FDA pointed out in the preamble to the proposed Regulations¹⁰⁶ and in the response to comments on the proposed Regulations (included with the final Regulations),¹⁰⁷ formulating a more precise rule would be almost impossible. The relevant inquiry is highly fact and situation-specific and hence not well suited to a fixed rule.¹⁰⁸

III. PROPOSED AMENDMENTS

In the years since 1983, Congress (and commentators) has perceived several problems with the Orphan Drug Act. The biggest problem by far, and one that manifests itself in several different ways, is the problem of "profitable orphans." The tax provisions have also been a source of frequent concern. To handle these perceived problems, Congress has proposed myriad Amendments to the Act.

A. Profitable Orphan Drugs

1. The Problem

Since the passage of the Orphan Drug Act, a few companies have taken advantage of its market exclusivity provisions to earn enormous profits on a few drugs. A wealth of commentary addresses this subject. However, when examined closely, the commentary all focuses on essentially the same four or five drugs: AZT (HIV

288; Kenney, *supra* note 102; see Carey & Hamilton, *supra* note 102.

104. See 57 Fed. Reg. 62076, 62077 (1992) (to be codified at 21 C.F.R. pt. 316) (issued Dec. 29, 1992) (response to comment 12); see also Rin-Laures & Janofsky, *supra* note 7, at 288; Kenney, *supra* note 102; see Carey & Hamilton, *supra* note 102; Arno et al., *supra* note 5, at 236-38 (including Table showing AIDS drugs used to "treat" and "prevent" the same condition).

105. 21 C.F.R. § 316.20(b)(6) (1998).

106. See 56 Fed. Reg. 3338, 3339-3340 (1991) (to be codified at 21 C.F.R. pt. 316) (proposed Jan. 29, 1991).

107. See 57 Fed. Reg. 62076, 62077, 62081 (1992) (to be codified at 21 C.F.R. pt. 316) (responses to comments 12 & 49).

108. The FDA also declined here, as elsewhere, to provide hypothetical examples, on the grounds that they were more likely to be misleading than helpful. See *id.*

infection/AIDS); pentamidine isethionate (pneumonia associated with AIDS); human growth hormone (hGH) (improper growth in children lacking the enzyme); erythropoietin (EPO) (anemia associated with end-stage renal disease); and Ceredase™ (Gaucher's disease).¹⁰⁹ The first two are chemical entities; the latter three are proteins. All of these drugs have been undoubtedly profitable, often recovering their development costs in the first year or two of sales. They also nicely illustrate the different aspects of the profitable orphan issue.¹¹⁰

a. Protected Profitability

Some orphan drugs have been profitable simply because they are protected from competition by the market exclusivity provision; Ceredase is a good example of this. Gaucher's disease is a classic orphan, and Genzyme, the holder of the exclusivity on Ceredase, did not have to manipulate the rules to get designation.¹¹¹ Furthermore, Genzyme almost certainly would not have developed Ceredase without the promise of market protection.¹¹² However, the protection from competition allows Genzyme to charge a monopoly price, and hence it makes huge profits on the drug.¹¹³

Ceredase draws so much attention because it is particularly difficult to manufacture, and thus its production costs are very high.¹¹⁴ When the monopoly rents are added on to this, the price appears particularly exorbitant. Estimates range as high as \$350,000 in the first year, and while the dosage can be reduced after the first

109. See, e.g., Arno et al., *supra* note 5; Dana P. Goldman et al., *Creating the Costliest Orphan: The Orphan Drug Act in the Development of Ceredase™*, 8 INT'L J. TECH. ASSESSMENT HEALTH CARE 583 (1992); Rin-Laures & Janofsky, *supra* note 7, at 279-289; Lawton, *supra* note 43, at 331-343; Carey & Hamilton, *supra* note 102.

110. In the midst of all this "greed," it should be pointed out that Bristol-Myers Squibb voluntarily relinquished its orphan drug designations for the AIDS drug Videx and the cancer agent Taxol, stating that it had "'learned more about the potential uses for the two drugs', and felt that retaining orphan status for them 'was not in keeping with the purpose of the act.'" *Orphan Drug Act at 10 Years: Rep. Waxman Prepared to Move Again on Amendments*, 55 F.D.C. REP. ("The Pink Sheet") (Mar. 1, 1993) (available on Westlaw in the FDC-RPTS database).

111. See Goldman et al., *supra* note 109, at 585 (Gaucher's disease probably afflicts at most 20,000 people in the U.S., Genzyme asserts only 3000 of whom warrant treatment.).

112. See Henri A. Termeer, *The Cost of Miracles*, WALL ST. J., Nov. 16, 1993, at A28 (Mr. Termeer is CEO of Genzyme); Goldman et al., *supra* note 109, at 588 ("[O]rphan designation was the impetus behind Genzyme's quest for FDA approval.")

113. Genzyme apparently recovered its development costs fairly quickly. See *Apology to Genzyme, Inc., for Overstating Current Profits from Orphan Drugs*, 139 CONG. REC. H1883-84 (daily ed. April 5, 1993) (noting initial investment of \$29 million recovered many times over).

114. See Goldman et al., *supra* note 109, at 589; see also *Apology to Genzyme, Inc.*, 139 CONG. REC. H1883 (daily ed. April 5, 1993) (manufacturing costs of \$1.90/unit).

year, the treatments must be continued for the life of the patient.¹¹⁵ Many patients are unable to afford this cost, and even those with insurance frequently exhaust that resource fairly quickly at this price.¹¹⁶ This situation has led to an outcry against Genzyme and the market exclusivity provision of the Orphan Drug Act.¹¹⁷

However, this outcry may be unwarranted. In the case of Ceredase, the Act seems to have worked exactly as it was intended to work: it gave Genzyme motivation to develop the drug, and Genzyme developed Ceredase.¹¹⁸ The difficulty of meeting the price is not a problem with the Orphan Drug Act, but with the general healthcare delivery system in the U.S.¹¹⁹ No patient is in a worse position because of the market protection. Those who cannot afford the drug are in the same position they would occupy if the drug had never been developed. Furthermore, at least some patients, those who can afford Ceredase, are in a better position. Many of the proposed changes to the Act would significantly change the incentive structure, with unpredictable results. Under an amended Act, Ceredase might well have never been developed and both patients and drug manufacturers would suffer.¹²⁰

This last point is important, as it is relevant to all of the problems discussed in this section, but it is often neglected by commentators. Many commentators treat the problem as a choice between having expensive drugs because of protection or having less expensive drugs by not protecting them. But the real tradeoff (unless one rejects the whole premise of the Orphan Drug Act and the need for its incentives, which few do explicitly)¹²¹ is between having expensive drugs and having *no* drugs for these diseases. As Robert K. Dresing, head of the

115. See Goldman et al., *supra* note 109, at 591.

116. See Larry Thompson, *The High Cost of Rare Diseases—When Patients Can't Afford to Buy Lifesaving Drugs*, WASH. POST, June 25, 1991, (Health), at 10.

117. Reps. Stark and Studds have repeatedly attacked Genzyme in the Congressional Record. See, e.g., 139 CONG. REC. H1883 (daily ed. April 5, 1993); 139 CONG. REC. H1851 (daily ed. April 1, 1993); 137 CONG. REC. E2435-37(daily ed. June 27, 1991).

118. See Termeer, *supra* note 112, at A28.

119. See Charles A. Sanders, *The Orphan Drug Act: Should It Be Changed?*, 153 ARCHIVES INTERNAL MED. 2623, 2625 (1993) (one of the few commentators to answer the title question "No") (Dr. Sanders is affiliated with Glaxo Corp.).

120. The Orphan Drug Act thus leads to a Pareto-superior outcome. See, e.g., RICHARD A. POSNER, *ECONOMIC ANALYSIS OF LAW* 13 (4th ed. 1992).

121. But cf. Flynn, *supra* note 10, at 395-96 (suggesting in an underhanded way that we might have gotten all those orphan drugs even without the Act, since we cannot tell now which were a result of the Act and which would have been developed anyway); *id.* at 443 (calling the market exclusivity provision "a form of discredited 1980s trickle down economic theory"); Arno et al., *supra* note 5, at 241 (questioning the need for marketing exclusivity as an incentive).

Cystic Fibrosis Foundation, said, "[P]aying even \$300,000 a year for an effective drug against cystic fibrosis would be preferable to having no drug at all!"¹²² Another important point that is often overlooked is that market exclusivity is merely *temporary*. The term of exclusivity is only seven years. Thus, in a fairly short time (although, of course, it seems too long to those who cannot afford the drugs), the market is open to as much competition as it can sustain. In fact, all of the drugs listed above that have ignited the controversy are now past their exclusivity period.¹²³

Henri Termeer, CEO of Genzyme, points out an interesting aspect of the Ceredase situation. The Act allowed Genzyme to make the first steps into this area, and Genzyme's success led to competition to develop other, less costly treatments.¹²⁴ Thus, the protected market for Ceredase had the effect of *increasing* competition in this market.¹²⁵

Another reason to accept the profitability of drugs like Ceredase is the general nature of the pharmaceutical industry. Because drug research is highly unpredictable,¹²⁶ successful drugs must subsidize the failures.¹²⁷ In the case of at least one company, Genentech, one blockbuster orphan drug (hGH) is viewed as subsidizing another drug, Actimmune (chronic granulomatous disease), that is not a

122. Gina M. Cavalier, *Pushing Parentless Pharmaceuticals: Toward an International Home for "Orphan Drugs" and a Cure for "Zebra" Diseases*, 27 LAW & POLY INT'L BUS. 447, 457 n.70 (1996) (quoting testimony before the Subcommittee on Antitrust, Monopoly, and Business Rights, *quoted in* Rex Rhein & Tony Delamothe, *Orphan Drugs*, 304 BRIT. MED. J. 465 (1992)). *But see id.* at 457 ("[I]t does not make sense to waste precious resources to develop a cure when sufferers cannot benefit from it because of prohibitive cost.").

123. *See* Arno et al., *supra* note 5, at 239 (pentamidine, 1996); Goldman et al., *supra* note 109, at 588 (Ceredase, 1998); Carey & Hamilton, *supra* note 102, at 38 (EPO, 1996; AZT, 1994; hGH, 1994); *see also* Paul V. Buday, *Hints on Preparing Successful Orphan Drug Designation Requests*, 51 FOOD & DRUG L.J. 75, 76 n.10 (1996) (noting that exclusivity has expired on 26 orphan drugs (as of Feb. 1996)).

124. *See* Termeer, *supra* note 112, at A28.

125. One potential flaw in this theory is that Gaucher's disease is still an orphan, and so the new treatments may also be protected. However, as with attempts to "design around" patents, these treatments may well be sufficiently different to warrant separate designation and so compete with each other. Alternatively, some of them will be so similar to Ceredase that they could compete when the exclusivity expired in 1998. *See* Goldman et al., *supra* note 109, at 588 (table showing FDA approval in 1991).

126. *See* Henry, *supra* note 22, at 617 ("For every 10,000 drug candidates created in the lab only 1,000 compounds will be tested in animals to reveal their pharmacological and toxicological characteristics. Of those 1,000 compounds, only one will end up on the pharmacist's shelf. Only one in five new compounds tested in humans is likely to reach the market.").

127. *See* Sanders, *supra* note 119, at 2624 (1993).

blockbuster.¹²⁸ Furthermore, the lure of developing a blockbuster is part of what keeps the game going. "If drug companies are told there will be no winners, these companies are unlikely to enter a game in which they cannot offset their losses."¹²⁹ Thus, large profits for a few drugs might be something to embrace, rather than avoid. This is especially true since so few (less than ten percent) of orphan drugs even approach blockbuster status.¹³⁰ Large profits for a very few drugs may be the price patients must pay (and should pay gladly) to have an orphan drug system that works as well as it does.

b. Losing the Race

Another problem cited by critics is the situation of firms racing each other for orphan drug approval. Some of these drugs were so likely to be successful that more than one company obtained orphan drug designation, in pursuit of the market exclusivity that would be granted to the first to complete clinical trials and get the drug approved for sale.¹³¹ This is viewed as a problem for two primary reasons. First, it calls into question the "orphan" status of the drugs; true orphans rarely have prospective parents fighting over them.¹³² The fact that firms are fighting over these drugs suggests that in fact they are likely to be profitable, and hence it is an abuse of the orphan drug incentives if they are applied to these drugs.¹³³

However, this argument rests on a faulty premise. It assumes that these companies would be racing anyway, and the incentives are therefore an unnecessary prize. An entirely plausible explanation is that the race is a race *for* the incentives of the Act. In fact, this is essentially the premise on which the exclusivity provisions rest: the provisions convert what would be a losing proposition (if copycats could take advantage of the work of the orphan drug pioneer) into a

128. See *id.* (quoting G. Kirk Raab, then-president and CEO of Genentech).

129. See *id.* (quoting G. Kirk Raab, then-president and CEO of Genentech).

130. See Shulman et al., *supra* note 38, at 402 (Table 11, indicating that only the top decile of drugs are taking in truly blockbuster revenues). In the time since this article, many more orphan drugs have been approved but there have been no reports of more blockbusters.

131. See Lawton, *supra* note 43, at 331 (discussing, *inter alia*, the approvals of hGH, EPO, and pentamidine).

132. Cf. James T. O'Reilly, *Orphan Drugs: The Strange Case of "Baby M"*, 42 FOOD DRUG & COSMETIC L.J. 516, 516 (1987) (analogizing these popular orphan drugs to Baby M, whose biological parents and adoptive parents fought over her custody).

133. See Meyers, *supra* note 32, at 11 (stating a drug should not be designated as an orphan unless the incentives of the Act are "absolutely essential to ensure its development," and indicating that multiple companies were unlikely to be interested in a drug that was truly of "limited" commercial value).

winning one (by granting the pioneer an exclusive market). The market exclusivity makes the market potentially profitable, and thus makes the drug worth racing for.¹³⁴ Races for approval may thus be interpreted as a sign that the Act is serving its purpose by giving drug companies incentives to develop otherwise unprofitable drugs. In most cases, distinguishing a race for orphan drug incentives from a race for a drug that would have been developed anyway is almost impossible, again pointing out the dangers of changing the Act. The effects on the races of any changes to the Act cannot be foreseen in advance. An amendment that changes the incentives could have adverse consequences for a highly successful piece of legislation.

The second difficulty with racing is that it wastes resources and that it can be very hard on the loser, who has invested a great deal of time and money but has not achieved any reward. These parameters and resolutions of this very complex issue are not clear. Further exploration of this issue is in the shared exclusivity discussion, contained in Part III.A.2.a, *infra*.

c. *Salami Slicing*

The next criticized abuse of the Act is the phenomenon of "salami slicing."¹³⁵ As mentioned above, salami slicing — the practice of dividing a medical condition into subsets containing fewer than 200,000 individuals and then obtaining exclusivity for each market — is a real problem under the Act. However, the extent of the problem and incidence of success of this strategy are not entirely clear. Critics present the case of EPO as the clearest demonstration of this problem.¹³⁶ Amgen obtained market exclusivity for using EPO to treat anemia associated with end-stage renal disease. However, EPO is also useful for treating a wide range of other anemias, and has even been designated for some of these other conditions.¹³⁷ It is also useful for treating patients with renal disease before it reaches end-

134. A large patent race literature supports this point. See generally Robert P. Merges & Richard R. Nelson, *On the Complex Economics of Patent Scope*, 90 COLUM. L. REV. 839 (1990), and references therein.

135. See *supra* note 102 and accompanying text.

136. See John M. Coster, *Recombinant Erythropoietin: Orphan Product with a Silver Spoon*, 8 INT'L J. TECH. ASSESSMENT HEALTH CARE 635, 636-37 (1992). Patients with end-stage renal disease have chronic kidney failure, and so their kidneys fail to produce endogenous EPO, which makes them anemic; giving them exogenous EPO helps alleviate this condition. See *id.* at 635.

137. See Arno et al., *supra* note 5, at 242; Shulman et al., *supra* note 38, at 371; Rin-Laures & Janofsky, *supra* note 7, at 281, 288.

stage.¹³⁸ Thus, Amgen appears to have sliced up the market for EPO into artificial submarkets and thereby obtained exclusivity inappropriately.¹³⁹

The right result in this case is not entirely clear. Ideally, since EPO would probably have been developed without the help of the Act, it should not be eligible for protection.¹⁴⁰ However, in some cases, dividing a market makes sense. For example, if a drug has particularly toxic side effects, it might only be appropriate for patients who have failed to respond to other, less toxic treatments (this particular argument would not apply to EPO).¹⁴¹ Devising a rule that would eliminate salami slicing and not discourage appropriate submarketing would be nearly impossible, as the two situations are difficult to distinguish, even with a detailed analysis.

The FDA has attempted to resolve this problem in the Regulations by stating that disease subsets must be "medically plausible."¹⁴² The effect of this rule on the EPO designation is not clear. The end-stage renal disease patients may be a medically plausible subset, or they may instead be the result of salami slicing. The same holds true for the other forms of anemia. To a large degree, this is a medical decision, with a dollop of policy thrown in. In the case of EPO, the obvious profitability of the drug should probably have been weighed against the grant of designation. However, the call is a close one and it is hard to find fault with the FDA's choice, considering the limited evidence available at that time and the FDA's limited experience with the Act.¹⁴³ With 16 years of experience in administering the Act, the FDA is now in a much better position to employ its "medically plausible" subset definition. Hopefully it can avoid the problems associated with approving a highly profitable drug like EPO.

138. *See id.*

139. *See Coster, supra* note 136, at 636. One of the main reasons that Congress is so concerned about the high price of EPO is that it is covered by Medicare and Medicaid, and thus the high price of EPO caused by its market monopoly impacts directly on the federal budget. *See id.*

140. *See Coster, supra* note 136, at 642.

141. *See* 56 Fed. Reg. 3338, 3339 (1991) (to be codified at 21 C.F.R. pt. 316) (proposed Jan. 29, 1991) (preamble to the FDA's proposed Orphan Drug Regulations).

142. *See supra* Part II.D.3.

143. The FDA has apparently tweaked the rules a little bit to help alleviate this problem and allow some competition in the EPO market. *See Coster, supra* note 136, at 641.

d. Expanding Orphan Diseases

The final problem cited by critics of the Orphan Drug Act is expanding orphan diseases. This term is used in discussing drugs that met the orphan condition of treating an indication that affected fewer than 200,000 people at the time they were approved,¹⁴⁴ but the indication later expands to affect more than 200,000 people before the period of marketing exclusivity ends. The paradigmatic example of this type of disease is AIDS, which is an infectious disease that has spread throughout the population. Many drugs that received orphan designation for conditions related to AIDS have become very lucrative as the market has expanded to encompass more and more people. AZT and pentamidine are two drugs that fit into this category.¹⁴⁵

Again, like salami slicing, the expansion of AIDS is a real problem. However, it arises in an unusual situation, one that (fortunately) is unlikely to be duplicated. Most orphan drugs treat conditions such as genetic diseases or cancers, which do not spread.¹⁴⁶ Furthermore, AIDS passed the 200,000 affected persons threshold in 1993, and so most AIDS-related conditions no longer qualify for orphan drug designation.¹⁴⁷ Barring another outbreak such as AIDS, this problem is unlikely to recur.^{148,149}

Some of the profitable drugs in this small group clearly fall outside the intent of the original Orphan Drug Act, which was designed to give incentives to drug companies so they would develop

144. This is all the Act requires. See 21 U.S.C. § 360bb(a)(2) (1994) (stating that eligibility is determined "on the basis of the facts and circumstances as of the date the request for designation of the drug . . . is made").

145. See Arno et al., *supra* note 5, at 238 (Table 1 presenting these and other AIDS-related orphan drugs).

146. See Shulman et al., *supra* note 38, at 370, 387 (Table 1 showing distribution of orphan drugs by disease class; only 19% in AIDS and other infectious diseases).

147. See Arno et al., *supra* note 5, at 240.

148. Another possible type of disease expansion is an improved diagnostic technique that suddenly increases the known afflicted population for an indication. This seems somewhat improbable; the sudden discovery of such a population requiring a drug treatment that is already available to the known patients with that indication, and protected, is unlikely. In any case, as discussed in Part III.A.1.a, *supra*, the problem would be temporary, ending at the latest in 7 years.

149. See Arno et al., *supra* note 5, use AIDS as a lens for viewing the Orphan Drug Act, and on so viewing concluded that it is cracked. However, it is the lens that is cracked, not the Act. AIDS is totally atypical of orphan diseases, and as such reveals very little about how the Orphan Drug Act works in general. But see Robert A. Hamilton, *Rare Disease Treatments: 'Orphans' Saving Lives*, FDA CONSUMER, November 1990, at 6, 8 (suggesting that the Orphan Drug Act did facilitate the development of AIDS drugs in the early years).

drugs that were otherwise unlikely to be developed (although as discussed *supra* they all arguably fit within the text of the Act). However, these drugs are the exception rather than the rule. This is most evident in the exceedingly thorough analysis of what has actually happened under the Act performed by Shulman et al.¹⁵⁰ Shulman et al looked at all of the data they could collect on the orphan drug designations and approvals that were granted during the first eight years of the Orphan Drug Act and analyzed that data in several different ways. Their results demonstrate overwhelmingly that the Act is achieving its intended purpose: getting drugs to people with rare diseases.¹⁵¹

2. The Proposed Solutions

Despite arguments to the contrary, the overwhelming majority of commentators and Congresspersons think that the Orphan Drug Act needs to be fixed. Consequently, a number of Amendments to the Act have been proposed over the years. However, none of these proposals have been implemented (except the changes discussed in Part II.B, *supra*). These proposed Amendments have attempted to change the Act in a variety of ways.

a. Shared Exclusivity

The most popular and controversial provision for changing the Orphan Drug Act is shared exclusivity.¹⁵² Shared exclusivity primarily addresses the racing problem. However, since it may serve to increase competition, it also addresses the problem of high prices and profits in general. Congress has proposed various Amendments that would have allowed two or more drug companies simultaneously developing an orphan drug to "share" the market exclusivity. In general, these Amendments allow drug companies that file for designation and approval within a certain length of time of each other

150. Shulman et al., *supra* note 38, at 363-403.

151. See, e.g., *id.* at 395-99 (Table 8 showing incidence of indications treated by approved orphan drugs; range is 1 to 184,000, skewed toward lower incidence). See also *id.* at 402 (Table 11 showing mean sales of orphan drugs by decile; large gap between top decile (4 drugs) and rest of distribution; distribution highly skewed toward lower sales); *id.* at 380 (reporting median sales for U.S. orphan drugs as \$1.6 million); see also Haffner, *supra* note 29, at 604 (Figure 1 showing breakdown of orphan drug designations by disease prevalence (1983-1990); 50% of drugs are for diseases affecting fewer than 25,000 people; 68% of drugs are for diseases affecting fewer than 50,000 people; 84% of drugs are for diseases affecting fewer than 100,000 people); Sanders, *supra* note 119, at 2623 ("[T]he Orphan Drug Act of 1983 . . . has done exactly what its supporters intended it to do.").

152. "Shared exclusivity" is an oxymoron, but it is the term used in the literature.

to each be granted the seven years of market exclusivity.

As early as 1986, Congress proposed to change the Act so that it would allow sharing of exclusivity when two drugs were developed "simultaneously." "Simultaneously" was defined as the later company submitting its application for approval before the earlier company's application was approved.¹⁵³ This bill failed to pass. The next attempt to provide for shared exclusivity occurred in 1990.¹⁵⁴ The Orphan Drug Amendments of 1990 proposed a more rigorous standard for simultaneous development. The later companies had to: (1) file the requests for designation within six months of the publication of the leader's designation; (2) start their clinical trials within twelve months of the leader; and (3) file for approval and request exclusivity within twelve months of the leader's filing for approval.¹⁵⁵ These strict requirements were intended to prevent copycat generic companies from appropriating the work of the leaders and then forcing the leaders to share their exclusivity. The requirements could help guarantee that the two companies were in fact simultaneously developing the orphan drug.¹⁵⁶ After President Bush pocket vetoed the 1990 Amendments, Congress reintroduced the same simultaneity provisions in the Orphan Drug Act Amendments of 1994, which were not enacted.¹⁵⁷

The shared exclusivity provisions would allow as many companies as developed the orphan drug within the given time window to share the market exclusivity. Three basic concerns drive

153. See 132 CONG. REC. S11944 (daily ed. Aug. 11, 1986) (statement of Mr. Hatch in the introduction of S. 2772).

154. See 136 CONG. REC. 20375, 20375 (1990) (H.R. 4638); H.R. REP. NO. 101-635, at 2-3 (1990). The amendment planned to make the shared exclusivity retroactive, thereby breaking up the monopolies of the blockbuster drugs; however, there was some dispute over whether this would be an "unconstitutional taking." See *Orphan Drug Bill Amendments Would Result in "Unconstitutional Taking,"* 52 F.D.C. REP. ("The Pink Sheet") (June 11, 1990) (available in Westlaw, FDC-RPTS database); 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, 144 (1995).

155. See e.g., 132 CONG. REC. S11944 (daily ed. Aug. 11, 1986) (statement of Mr. Hatch in the introduction of S. 2772). These standards would put a drug developer into an interesting quandary over when to file for designation. Current practice is usually to wait until the last minute, just before filing for approval. See Buday, *supra* note 123, at 79. This approach has the advantage of giving other companies as little notice as possible of the filing. However, under shared exclusivity, early filing would have the advantage of potentially discouraging other companies from competing, since the early filing exerts pressure to meet the deadlines. Which of these strategies would win out is not obvious to me.

156. See 136 CONG. REC. 20375, 20377 (1990) (comments of Rep. Nielson).

157. See 140 CONG. REC. S3685-01, S3728 (daily ed. Mar. 24, 1994) (statement of Sen. Kassebaum).

these sharing provisions: (1) allow competition so the price is reduced; (2) avoid the wasting of resources that occurs when two companies race for a prize that only one can obtain; and (3) prevent force the "losing" company that has made a huge investment of time and money (perhaps without even knowing it was in a race) from going away with nothing.¹⁵⁸

The premise that shared exclusivity automatically leads to price competition and therefore to significantly lower prices is somewhat questionable in the drug market. Historically, the rise of the pharmaceutical industry was founded on intellectual property protection (primarily product patents), which enabled competition based on innovation rather than price.¹⁵⁹ The principle of shared protection and price competition is thus largely foreign to the drug market, and allowing shared exclusivity is therefore unlikely to have the desired effect on drug companies. Furthermore, even if shared exclusivity generates actual competition, it may not significantly reduce prices. The experience with hGH, which is essentially a shared exclusivity between Genentech and Eli Lilly,¹⁶⁰ demonstrates this point: despite the competition, hGH is still one of the highest priced and most profitable orphans, for both companies.¹⁶¹ Moreover, even before the Act, orphan products were already more costly than average drugs, regardless of development cost,¹⁶² and thus competition may not reduce prices significantly.

For the other two concerns, shared versus absolute exclusivity raises many difficult issues. Orphan drug exclusivity racing is in many ways analogous to patent racing, and so the patent race literature is instructive on these issues.¹⁶³

158. See Rin-Laures & Janofsky, *supra* note 7, at 286-87; Kenney, *supra* note 102, at 675-76.

159. See Carolyn H. Asbury, *The Orphan Drug Act: The First 7 Years*, 265 JAMA 893, 896 (1991); Sanders, *supra* note 119, at 2624 (both making this point and citing Temin, *supra* note 25, for the observation that drug companies compete on innovation rather than price).

160. The two products differ by a single amino acid, but because they have different sources, the FDA at the time (before the Regulations went into effect) decided that they were different products; however, for all practical purposes, the drugs are identical. *But see* Genentech, Inc. v. Bowen, 676 F. Supp. 301, 311-13 (D.D.C. 1987) (discussed *infra* Part IV.D). The two products would almost certainly be deemed the same under the Regulations. See *supra* Part II.D.2.

161. See Arno et al., *supra* note 5, at 246 (discussing hGH and suggesting that "shared exclusivity may be insufficient to lower orphan drug prices[, which] is certainly counterintuitive and implies imperfections in the pharmaceutical marketplace").

162. See Asbury, *supra* note 159, at 896.

163. See generally Merges & Nelson, *supra* note 134, and references therein. Interestingly, comparisons between patents and orphan drug exclusivity may provide insight back into patent

One issue is the effect of shared exclusivity on efficient cooperation. Shared exclusivity could lead to either more cooperation or to less. In a winner-take-all race, each side has the incentive to cooperate so that it does not risk losing completely. On the other hand, depending on its risk tolerance and perceived standing in the race, a company may be willing to risk being shut out for the chance to take everything. Conversely, with shared exclusivity, the pressure to cooperate is reduced, because the cost of losing is minimal; the company will share in the prize if it finishes close. However, the pressure to compete is similarly reduced, since the prize is much less valuable because it is not absolute. Therefore, cooperating from the start might make more sense since the prize will probably be shared anyway.

Another factor that enters into this analysis is cost. Cooperative research is likely to cost less than individual research, since competitors almost always must duplicate at least part of each other's work. Under these conditions, shared exclusivity will almost certainly lead to cooperation, because a company will obtain essentially the same prize either way and the costs will be less with cooperation. The question then shifts to whether cooperation is the most efficient way to get results. In the specific case of competing for orphan drug approval of the same drug for the same condition, competing firms are likely almost always to be duplicating each other's work, rather than pursuing alternative strategies. Once researchers know that the drug has some efficacy for the orphan disease, all those companies in the race will be performing essentially the same trials to get approval for use in humans.¹⁶⁴ Thus, races would seem to be inefficient duplications of effort, and cooperative efforts are favored.¹⁶⁵

A related way to encourage cooperation is to award a bigger prize if it must be shared; in the context of the Orphan Drug Act, this

racers. If Congress ever enacts shared exclusivity, a study of the resulting effects on the market will provide particularly valuable information.

164. See Suzanne Scotchmer, *Patents as an Incentive System*, PROC. INT'L ECON ASSOC., Sept. 1992, at 281, 285 (discussing inefficient duplication of costs).

165. See Steven R. Salbu, *AIDS and Drug Pricing: In Search of a Policy*, 71 WASH. U. L.Q. 691, 701-02 (1993) (discussing disadvantages of the "winner-take-all mentality in drug research"); cf. *id.* at 708-09 (noting that the principles of patent policy are not inviolate "natural economic laws" and should be examined critically). See also Manfredi La Manna et al., *The Case for Permissive Patents*, 33 EUR. ECON. REV. 1427, 1436 (1989). (The authors argued that a patent system with multiple prizes might be preferable to a strict (i.e., single-winner) regime, although they concluded that when inventions are "difficult" (which would seem to apply to drug research, see *supra* note 126), the strict regime may be socially preferable.)

could be accomplished by increasing the length of the shared exclusivity term. This idea is sometimes presented as a quid pro quo for denying the absolute exclusivity, or as a way to give all the sharing companies a chance to recover their investments (since they must sell at a lower price because of the competition),¹⁶⁶ but it will also function as a cooperation incentive.

The remaining cooperation issue is whether or not getting a shared (and hence smaller) prize, obtained at a potentially lower cost, is a worthwhile trade-off. Drug companies may perceive that it is no longer worth competing for shared exclusivity.¹⁶⁷ One particular worry is the interference of the antitrust laws, which might prevent cooperation in some situations.¹⁶⁸ Having a shared prize while being forbidden to cooperate would be the worst possible outcome, as the costs would be the same as with winner-take-all competition, while the rewards would be less.

Facilitating cooperation, however, is not the only or even primary consideration for analyzing shared exclusivity. Shared exclusivity in many respects appears to a potential drug producer as practically indistinguishable from straight competition. The producer would be unable to analyze in advance the possibilities of entry by competitors into the market, which would be equivalent to competition. Given the fact that drugs in general, and orphan drugs in particular, are already risky investments, the uncertainty could easily lead to investment at less than the optimal level. In many cases, the market for an orphan drug is likely to be marginal at best, with only a monopolist being able to make a profit. In a marginal market, firms that enter because exclusivity makes the investment worthwhile will be unwilling to do so if they risk gaining only an unprofitable partial market. Even if a shared market were potentially profitable, the increased uncertainty and difficulty of the forecasting calculations might still make firms unwilling to take the risk of investing. This uncertainty of risks in a shared market is exactly the problem that faced drug companies before the Orphan Drug Act, and was in fact the reason the Act was passed in the first place.

The most important drawback to shared exclusivity is the incentive it would give drug companies to manipulate the designation

166. See Clissold, *supra* note 154, at 145; Rin-Laures & Janofsky, *supra* note 7, at 286-87.

167. The history of the drug industry suggests that they may be reluctant to compete without an exclusive reward. See *supra* note 159 and accompanying text.

168. See Clissold, *supra* note 154, at 145; see generally Thomas M. Jorde & David J. Teece, *Innovation, Cooperation and Antitrust*, 4 HIGH TECH. L.J. 1 (1989).

process, and the corresponding enormous administration costs it would impose on the FDA in trying to prevent such manipulation. As the orphan drug system currently operates, drug companies may file for designation with relatively little initial cost and little ongoing burden. The FDA is not required to do extensive investigation and monitoring of the designees, because designation does not convey particularly large benefits. Designation does entitle the designee to tax benefits, protocol assistance, and grants; however, as discussed *supra*, experience has demonstrated that the primary benefit under the Act is the market exclusivity, which the manufacturer can only obtain after the drug goes through the normal drug approval process.

Under the proposed shared-exclusivity regime, designation assumes an entirely new importance. The mere grant of designation starts a six-month clock running for all other potential designees. If a company does not file within this time, it is essentially barred from pursuing the designated drug for that indication. Once the six-month window is closed, any later company faces a losing position: if it loses the race to develop the drug, it will be excluded from the market; if it wins the race, the original designee still has a year to catch up and share the exclusive market.¹⁶⁹ The original designee is thus under very little pressure to proceed quickly, since it knows that another company is unlikely to start a development program under these conditions.

Under the existing rules, the designation benefits of grants, tax credits, and protocol assistance are only valuable for a company actively pursuing the orphan drug. A shared-exclusivity system, however would greatly increase the value of designation, since the potential for excluding others or at least sharing in their market has value in itself, regardless of the activity level of the company's drug-development program. Thus, even if the company has no current plans to develop an orphan drug, it will still have the incentive to get designation, to protect the potential future market and perhaps prevent competitors from even starting research and development.

As the system for designation currently stands, companies have little disincentive to engage in this type of behavior. The Act does require that a company inform the FDA of "any decision to

169. The one-year bar that starts running once the FDA grants exclusivity does prevent the worst form of manipulation, which would be to file for designation and then let another company develop the drug, only joining in the exclusivity if the drug proves profitable; completing clinical trials in less than one year is impossible. The date bars as a whole similarly exclude generic competition.

discontinue active pursuit of approval" of a designated orphan drug,¹⁷⁰ and the FDA Regulations require annual reports from holders of designations.¹⁷¹ However, these requirements suffer from serious drawbacks. For one, "active pursuit" is not defined as any particular level of research activity, and any company wanting to avoid the notification requirement could easily maintain some minimal level of research that would arguably qualify. More importantly, neither of these rules contains any provisions for enforcement. The most effective sanction would be the revocation of designation. The Act is silent on this point, but the Regulations are very specific on the reasons for which a designation may be revoked — and these reasons do not include failure of active pursuit or annual reporting.¹⁷² Congress could also provide the FDA with other ways to punish companies for obtaining designation and then failing to pursue approval.

Without a procedure for the revocation of designation or other punishment, drug companies have no incentive to refrain from obtaining designation as a weapon against competitors. However, the Amendments proposed by Congress do not contain these provisions for punishment. Furthermore, any proposed punishment scheme would place a large enforcement burden on the FDA. Companies with designations are very keen to preserve them, and any attempt to revoke a designation would almost certainly require a hearing to comport with due process.¹⁷³ The FDA would need to draft a set of standards for what constituted "active pursuit" and then enforce it rigorously. Most revocations would probably then have to be defended in court. The administrative costs of maintaining a viable system of shared exclusivity while preventing game playing would be huge, and these costs are likely to far outweigh any gains from price reduction due to competition. Any system of complex rules would also itself be a disincentive to a company considering orphan drug development, potentially leading the company to decide that the hassle is just not worth the potential reward.

170. 21 U.S.C. § 360bb(b)(2) (1994).

171. See 21 C.F.R. § 316.30 (1998).

172. See *id.* § 316.29 (revocation only for untrue or omitted information in the request for designation).

173. Cf. 136 CONG. REC. 20375, 20375 (1990) (H.R. 4638). The amendment planned to make the shared exclusivity retroactive, to break up the monopolies of the blockbuster drugs; however, there was some dispute over whether this would be an "unconstitutional taking," and the retroactivity provisions were deleted in committee. See *Orphan Drug Bill Amendments Would Result in "Unconstitutional Taking," supra* note 154; Clissold *supra* note 154, at 144.

Furthermore, the Act and Regulations give competitors no indication of the credibility of a designee's research program. In fact, the Regulations are quite particular that only the fact of designation (including the sponsor, drug name, and condition treated) is made available to the public. Thus, competitors have no way of judging whether or not the designee is in fact actively pursuing the drug or is merely holding onto the designation as a weapon. Without the ability to monitor the progress of the designee, the competitors cannot gauge the intensity of the threat posed by this weapon and thus cannot properly assess whether or not to pursue the orphan drug. This unpredictability of the competitive position is likely to make drug manufacturers very nervous about committing resources to orphan drug development, effectively destroying the incentive scheme established by the Act.

Thus, while a change in the Orphan Drug Act to allow shared exclusivity might enhance cooperation and seem more "fair" to losers, the severe damage to the Act's incentives and the enormously increased administration costs weigh against enacting any such change. Given the success of the Act as it currently exists, the potential gains from shared exclusivity are not worth the risks that tampering with the Act might bring.

A variation on the shared exclusivity theme appeared in the 1987 Amendments. These amendments proposed to make the exclusivity apply only against generic drug applications.¹⁷⁴ These "me-too" applications allow generic drug companies to take advantage of the clinical data collected by the original manufacturer, using this data to get approval of a bioequivalent drug.¹⁷⁵ Under the proposed 1987 Amendments, any company that collected all of the data needed for approval could get the approval and protection from generic competition. Thus, in true race situations where two companies were independently gathering data, both could get approval and protection from generic competition — but not from each other. In some respects, this would resemble the protection provided by the Drug Price Control and Patent Term Restoration Act (DPCPTR Act), which made these generic applications possible but also provided periods of

174. See 133 CONG. REC. E3724-25 (daily ed. Sept. 29, 1987) (introduction of H.R. 3349 Orphan Drug Amendments of 1987). The remainder of the provisions of the 1987 Amendments were enacted as part of the Orphan Drug Amendments of 1988. See also Meyers, *supra* note 32, at 11-12 (arguing that protection from generic competition was actually what was intended in the original Act).

175. See 21 U.S.C. § 355(j) (1994) (Abbreviated New Drug Application (ANDA) provisions).

market exclusivity against generic competitors for new drug approvals.¹⁷⁶ However, the objections to shared exclusivity discussed in this part apply even more convincingly to a system that lacks even a time-based bar to entry, and so Congress should not revive these Amendments.

b. Changed Exclusivity Term

Another popular proposal is to change the length of the term of exclusivity. Various numbers have been proposed. The Orphan Drug Act Amendments of 1994 proposed reducing the term to four years, but with the opportunity to extend it to seven years if the holder of exclusivity could prove that it was a drug of "limited commercial potential."¹⁷⁷

The Orphan Drug Amendments of 1992 were a little more complicated, because the change in the exclusivity term was accompanied by a sales cap. An approved orphan drug was guaranteed exclusivity for a period of two years. After two years, if at any time during the next seven years, the total revenue from the orphan drug exceeded \$200 million, the exclusivity term would be revoked.¹⁷⁸ Thus, the Amendments extended the term for most orphan drugs to nine years, while reducing the term on the most successful drugs to as little as two years. The authors of the Amendments believed that this change to the Act would not seriously affect the operation of the Act as ninety-seven percent of orphan drugs never even approach the \$200 million threshold.¹⁷⁹ They further argued that no company would decline to market an orphan drug product just because it would face competition after its sales reached \$200 million.¹⁸⁰ Neither the 1992 nor the 1994 Amendments were brought to a vote in Congress.

The Biotechnology Industry Organization (BIO), an umbrella group for many biotechnology companies, proposed reducing the

176. See Drug Price Competition and Patent Term Restoration Act, Pub. L. No. 98-417, 98 Stat. 1585 (codified as amended at 21 U.S.C. § 355(c)(3) (1994)) (market exclusivity provisions).

177. See 140 CONG. REC. S3684, S3728 (daily ed. March 24, 1994) (statement of Sen. Kassebaum discussing the provisions of the Orphan Drug Act Amendments of 1994, S. 1981 & H.R. 4160).

178. See S. REP. NO. 102-358, at *2 (1992) (1992 WL 193619) (report on S. 2060 Orphan Drug Amendments of 1992). The Amendments also provided transition rules for approved and pending orphan drugs, as well as challenge provisions for manufacturers who wished to prove that their costs had not been recovered at \$200 million. See *id.* at *8.

179. See *id.* at *2.

180. See *id.* at *6.

term to five years, with the opportunity to apply for a five-year extension if the drug had "limited commercial potential." To be eligible for the extension, the drug would need to be for a disease that affected fewer than 100,000 patients.¹⁸¹ This proposal was never formally introduced in Congress, but it may have influenced the 1994 Amendments.¹⁸²

The main problem with these amendments is that they return to the failed system of the 1983 Act, which tried to force drug companies to release development costs to get protection. Thus, the effect of the 1994 provisions would be to reduce the incentive to a four year market exclusivity provision, as drug companies will be reluctant to apply for the extra three years. The situations are not entirely analogous, as the 1983 Act required the projection of future costs while the 1994 Amendments only required information about incurred costs. However, these costs are still very difficult to compute, particularly if the drug is being investigated for more than one indication or disease, or in more than one country, and the costs must be allocated among the indications and countries. Drug makers also have a difficult time allocating overhead costs, and the crucial issue of recouping the costs incurred in developing drugs that ultimately fail as pharmaceuticals remains unresolved.¹⁸³ All of these factors are likely to have the effect of forcing drug companies to view the market exclusivity as a four-year term, which would have grave consequences on the incentive structure. The BIO proposal suffers from a similar difficulty.

The provisions of the 1992 Amendments are more in the nature of a revocation of exclusivity, and therefore will be discussed in the next part.

c. Revocation of Exclusivity

A third popular type of amendment is the revocation of exclusivity based on a trigger event. One type of proposed trigger event is keyed to achieving a given level of either sales or profits. Profit measures are notoriously difficult to compute and enforce, especially since drug companies prefer to keep this information

181. See *Orphan Drug Amendment Proposal Reduces Market Exclusivity*, 55 F.D.C. REP. ("The Pink Sheet") (June 21, 1993) (available on Westlaw, FDC-RPTS database).

182. See 140 CONG. REC. S3684, S3728 (daily ed. March 24, 1994) (statement of Sen. Kassebaum indicating the support of BIO for the Amendments which contained similar wording to the BIO proposal).

183. See Scotchmer, *supra* note 164, at 282, 287 (stressing the need to account for R & D failures in determining intellectual property protection).

secret, and therefore drug companies are unlikely to use any system that requires them to reveal it.¹⁸⁴ Levels of sales, however, are much easier to track and less likely to make drug companies nervous.¹⁸⁵ The 1992 Amendments proposed a sales level of \$200 million as an appropriate trigger event.¹⁸⁶

Although sales triggers are much easier to administer than profit triggers, they are also much less accurate. Drugs vary greatly in their development, production, and incidental costs (see the discussion of the very expensive drug Ceredase in Part III.A.1.a, *supra*), and so a sales cap will have very different effects on different drugs. A profit cap accounts for these differing cost levels and thereby puts each drug developer in the same relative position. One commentator, Sanders, asks, "Is a \$200 million [sales] cap fair for the company that invests \$195 million in development, when it applies equally to the company that invests \$50 million?"¹⁸⁷ The amount at which the cap is set is also questionable. Given the average cost to develop a new drug is \$360 million,¹⁸⁸ is a \$200 million cap reasonable? If the proposed cap is too low, then it runs up against the same problem as the split exclusivity term: it destroys the incentive structure of the Act because drug companies will only be able to earn profits if they provide cost and profit information to the FDA to demonstrate that they have spent more than the cap, and drug companies are reluctant to do anything that requires them to provide this data to the FDA.¹⁸⁹

Alternatively, an increase in the affected population to more than 200,000 people might be the trigger event. This provision has proved quite popular (it appeared in the Amendments of 1990,¹⁹⁰ 1991,¹⁹¹

184. This is especially true in this era of frequent Congressional discussions of price controls on pharmaceuticals. See, e.g., 139 CONG. REC. H658-59 (daily ed. Feb. 17, 1993) (excerpt of debate on establishing a Prescription Drug Price Review Board).

185. See 137 CONG. REC. S18366-67 (daily ed. Nov. 26, 1991) (statement of Sen. Kassebaum on S. 2060 Orphan Drug Amendments of 1991 (later the Orphan Drug Amendments of 1992)) (discussing the sales/profits distinction).

186. See S. REP. NO. 102-358, at *2 (1992) (1992 WL 193619) (report on S. 2060 Orphan Drug Amendments of 1992).

187. Sanders, *supra* note 119, at 2624.

188. See Anders, *supra* note 24, at B1.

189. See *supra* Part III.A.2.b. The relatively small size of the cap might not be a real problem for orphan drugs, since they have cost advantages provided by the Act's other incentives (tax credits, grants, protocol assistance) and the clinical tests require smaller populations. See *supra* text accompanying note 26.

190. See H.R. REP. NO. 101-635, at *4 (1990) (1990 WL 259270) (report on H.R. 4638 Orphan Drug Amendments of 1990).

191. See 137 CONG. REC. S18366-67 (daily ed. Nov. 26, 1991) (remarks of Sen. Kassebaum introducing S. 2060 Orphan Drug Amendments of 1991).

1992,¹⁹² and 1994¹⁹³), probably because it is congruent with the Act's basic presumption that drugs for conditions that affect more than 200,000 people will be profitable. Intuitively, the time at which this occurs should not matter to the presumption; either enough people are affected or they are not.

A related type of amendment, which might be viewed as somewhat of a "pre-approval revocation," is a requirement that orphan disease-affected populations be projected three years into the future. This provision appeared in the same group of Amendments as the population trigger.¹⁹⁴ Both of these provisions are essentially aimed at the expanding orphan diseases discussed in Part III.A.1.d, *supra*. They are intended to prevent AIDS-type situations, where everyone could see that (tragically) the affected population would cross the 200,000 barrier in a few years, resulting in presumably profitable drugs, but the FDA was powerless to stop issuing designations under the terms of the Act.¹⁹⁵

These provisions seem to be reasonable enough; they are unlikely to change the Act's incentive structure significantly. The three-year projection requirement makes particular sense, as it would have reduced the problem with profitable AIDS orphans much faster. As indicated earlier, these amendments comport with the assumption underlying the use of the 200,000 figure in the first place. As commentators Rin-Laures & Janofsky have indicated, a manufacturer that will have its exclusivity revoked because the affected population has passed 200,000 should be allowed to demonstrate that the drug remains unprofitable at the higher population, as is provided in the Act itself,¹⁹⁶ so as to preserve its exclusivity.¹⁹⁷

d. Windfall Profit Taxes

Another approach for limiting the profitable orphans (regardless of why they are profitable) is a windfall profit tax on all revenues above a certain level. This approach is particularly popular with Representative Stark from California, who introduces variations on it

192. See S. REP. NO. 102-358, at *3 (1992) (1992 WL 193619) (report on S. 2060 Orphan Drug Amendments of 1992).

193. See S. REP. NO. 103-366, at *2 (1994) (1994 WL 514508) (report on S. 1981 Orphan Drug Amendments of 1994).

194. See references cited *supra* notes 190-193.

195. See 21 U.S.C. § 360bb(a)(2) (1994) (population measured as of date of request for designation).

196. See 21 U.S.C. § 360bb(a)(2)(B) (1994).

197. See Rin-Laures & Janofsky, *supra* note 7, at 281.

at regular intervals.

The first proposal was the Orphan Drug Windfall Profits Tax of 1990.¹⁹⁸ This proposal allows drug companies to recapture twice the development costs of the orphan drug plus a twenty-five percent profit before the windfall profit tax goes into effect.¹⁹⁹ "The figure of 25 percent is chosen because it is a comfortable estimate of the average market profit for the brand prescription drug industry."²⁰⁰ Rep. Stark reintroduced the same bill the next year as the Orphan Drug Windfall Profits Tax Act of 1991,²⁰¹ and a changed version of the bill later in 1991.²⁰² This changed version of the bill called for a seventy-five percent tax on all profits once development costs had been recovered (leaving the manufacturer with a twenty-five percent profit). Finally, in 1993, Rep. Stark introduced a modified version of this latter windfall tax proposal again.²⁰³ The modified proposal called for a windfall profit tax of seventy-five percent on all profits over 125% of production costs, but only after all development costs had been recovered. None of these windfall tax proposals appears to have generated much support within Congress.

In theory, a windfall profit tax seems like a good way to accomplish what Rep. Stark intended to accomplish; it limits the profits on orphan drugs. However, once again these proposals run contrary to the practices of drug companies which work very hard to keep information like this confidential. It also, once again, brings out the need to account for developmental, production and marketing costs — the cumbersome provision that led to the failure of the original Orphan Drug Act.²⁰⁴ Further, the tax has a similar dampening effect as a sales cap although it does meet the objection of limiting everyone equally. Finally, a less-than-100% tax leaves the manufacturer with the incentive to charge high prices, which may even lead to higher prices as the tax is passed along to consumers.²⁰⁵

198. See 136 CONG. REC. H6194 (daily ed. July, 31, 1990) (remarks of Rep. Stark introducing the Orphan Drug Windfall Profits Tax Act of 1990).

199. See *id.*

200. *Id.*

201. See 137 CONG. REC. E1171 (daily ed. April 10, 1991) (remarks of Rep. Stark reintroducing the Orphan Drug Windfall Profits Tax Act of 1991).

202. See 137 CONG. REC. H7777 (daily ed. Oct. 10, 1991) (remarks of Rep. Stark introducing a new version of the Orphan Drug Windfall Profits Tax Act).

203. See 139 CONG. REC. H1851 (daily ed. April 1, 1993) (remarks of Rep. Stark regarding amendments to the Orphan Drug Windfall Profits Tax Act).

204. See Rin-Laures & Janofsky, *supra* note 7, at 284-85.

205. See *id.* at 285.

3. The Orphan Drug Amendments of 1990

Congress passed the Orphan Drug Amendments of 1990.²⁰⁶ The Amendments would have implemented shared exclusivity, revocation of exclusivity if the target population passed 200,000 people, projection of population for three years, and other miscellaneous changes. However, the Amendments passed late in the session, and President Bush pocket-vetoed them. In his Memorandum of Disapproval, he stated:

I have serious concerns about the effect H.R. 4638 would have upon the incentives of drug companies to develop orphan drugs. I believe we must not endanger the success of this program, which is due to large measure to the existence of the "market exclusivity" provision in the Orphan Drug Act that allows companies to have exclusive marketing rights to an orphan drug for 7 years. Weakening the current 7-year exclusivity period would certainly discourage development of desperately needed new orphan drugs.²⁰⁷

B. Ineffective Tax Credits

1. The Problem

The Orphan Drug Act provides a tax credit for fifty percent of the amount of money spent on clinical trials.²⁰⁸ The problem with the tax credit is the opposite of the problem with the market exclusivity — it is not working well enough. Several aspects of the drug industry and specific provisions of the tax credit interact in a way that makes the credits ineffective. First, the credit applies only to human clinical trials, not to animal trials, which are also very expensive. Second, the credit cannot be carried forward to future tax years or backward to past tax years. This is a particular problem for small biotechnology companies, which often have no revenue and therefore no tax liability while they are carrying out the research that qualifies for the credits; without taxes to pay, tax credits are worthless. Similarly, the credit is not refundable, which would be an alternative way to get the money to biotechnology companies having no tax liabilities.²⁰⁹ Finally, the

206. See H.R. REP. NO. 101-635, at *4 (1990) (1990 WL 259270) (report on H.R. 4638 Orphan Drug Amendments of 1990).

207. 137 CONG. REC. H73-74 (daily ed. Jan. 3, 1991) (H.R. 4638-Memorandum of Disapproval).

208. See 26 U.S.C. § 45C (Supp. II 1994).

209. See Rin-Laures & Janofsky, *supra* note 7, at 295 (discussing all these difficulties);

provision granting the credit requires that the company be "carrying on a business," which again may be problematic for small biotechnology companies that do not yet have products to sell. Another problem, not unique to the drug industry, is that the credit needs periodic legislative renewal, but Congress does not always renew it promptly and the credit occasionally lapses.²¹⁰

2. The Proposed Solution

Congress has chosen to solve several of these problems in direct fashion. First in 1995,²¹¹ and now again more recently,²¹² bills were introduced to make the tax credit permanent and allow the credit to be carried backward or forward. These Amendments will certainly make the tax credit more effective and more reliable.

IV. CONSTITUTIONALITY, PERSONALIZED DRUGS, AND OTHER ECLECTIC FRAGMENTS

A. Constitutionality

John Flynn has made the interesting argument that the Orphan Drug Act is an unconstitutional exercise of the patent power.²¹³ He argues that Congress has used the commerce clause to grant a patent-type right that could not be granted under the patent clause, which makes the Act an impermissible evasion of the patent clause. Since many of the approved orphan drugs are already known to be effective for the illnesses they treat, they cannot qualify as a "discovery" as required under the patent clause, and hence the granting of a patent-type right is unconstitutional.²¹⁴

Flynn may be correct in his analysis. However, without going into the problem in any real depth, an alternative possible interpretation is possible. Flynn essentially interprets the

Clissold, *supra* note 154, at 145; see generally David M. Richardson, *The Orphan Drug Tax Credit: An Inadequate Response to an Ill-Defined Problem*, 6 AM. J. TAX POL'Y 135, 180-86 (1987).

210. See 26 U.S.C. §§ 45C(e)(1), 45C(e)(2) (Supp. 1994) (credit lapsed between Dec. 31, 1994, and July 1, 1996; credit expired again May 31, 1997).

211. See 141 CONG. REC. E939 (daily ed. May 3, 1995) (remarks of Rep. Nancy Johnson introducing the Orphan Drug Tax Credit Amendments of 1995).

212. See 143 CONG. REC. E550 (daily ed. March 21, 1997) (remarks of Rep. Nancy Johnson); 143 CONG. REC. S1191-92 (daily ed. Feb. 10, 1997) (introducing S. 293).

213. See Flynn, *supra* note 10. From the tone of the article, Flynn just does not like the Act and has found a novel way to attack it.

214. This is a gross simplification of a very complex argument.

constitutional patent clause as including all the terms of the patent statutes, incorporating their precise statutory definitions as interpreted in judicial decisions. However, this reading is not necessarily compelled by the Constitution. Stepping back and taking a more liberal view of "discovery," for the limited purpose of the Orphan Drug Act, the holder of the exclusive marketing right has arguably "discovered," via clinical trials, that the compound is safe and effective in humans. Before the trials, the drug is not allowed to be used in humans; after the trials, it is. Arguably, the drug that is shown to be safe and effective in people is "new" relative to the drug before it was so shown. The investigator has certainly "discovered" *something* new. It might be debatable whether or not that "discovery" is sufficiently "new" to satisfy the constitutional imperative, but the argument that it is "new" is at least plausible.²¹⁵

B. Impact of "Personalized Drugs"

A recent article in *Science* raises a whole new set of questions about the future of the whole orphan drug program.²¹⁶ The article describes "pharmacogenetics," which is the science of linking people's genes to the differences in the way they respond to drugs. The ultimate goal of pharmacogenetics is to tailor drugs to specific genetic subgroups of the population, thereby increasing their effectiveness. The article presented the concern of some drug companies that "pharmacogenetics will shrink the market for a particular drug by limiting who can take it."²¹⁷ This statement raises the specter of a day when essentially *all* drugs are "orphans" under the current definition. Pharmacogenetics is a long way from achieving this end, if it can be achieved at all, but the possible implications for the Orphan Drug Act are fascinating.

C. The "Off-Label Use" Issue

A common concern raised by many commentators is that a drug that is approved and has exclusivity for an orphan disease indication will be found to have a significant off-label use that will drastically

215. For a related argument on the difficulties with applying the standard patent requirements to biotechnology inventions see Karen I. Boyd, *Nonobviousness and the Biotechnology Industry: A Proposal for a Doctrine of Economic Nonobviousness*, 12 BERKELEY TECH L.J. 311 (1997) (arguing for a doctrine of "economic nonobviousness" rather than "technical nonobviousness" in biotechnology).

216. See Jon Cohen, *Developing Prescriptions with a Personal Touch*, 275 SCIENCE, Feb. 7, 1997, at 776.

217. *Id.*

increase its market size. Because it has market exclusivity, the story goes, the maker will not attempt to get approval for the off-label use because the second market would not be protected, and competition in this second market would destroy the exclusivity in the orphan market as well.²¹⁸ However, if the off-label indication really represents a viable market, another company will certainly step in to serve it, obtaining FDA approval for its own version of the drug for this second indication. In the process, the original orphan market will also be destroyed, because the market exclusivity provision cannot be used to stop the sale of drugs approved for the second indication for off-label use on the orphan indication. Thus, a viable off-label use should actually serve to *increase* competition. The only time this might not occur would be if the second market was too small to justify anyone's effort to get approval. However, then by definition it would be an orphan market, and the off-label use would be an orphan use — and this type of use would certainly not be inconsistent with the Act. Thus, the concern over off-label use is not justified and should not be considered a valid argument against market exclusivity.

D. Cases

Most of the battles surrounding the Orphan Drug Act have been fought in Congress, the FDA, or scholarly journals, and very few cases have reached the courts. The first case to do so was *Genentech v. Bowen*.²¹⁹ *Genentech* discussed the Act and its history at great length in deciding that the recombinant hGH made by Eli Lilly, Genentech's rival, was not the "same drug" as the old cadaver-derived hGH that already had FDA approval (the case did not hold, as some commentators report, that Lilly's hGH was different from Genentech's hGH by virtue of being one amino acid shorter; the court expressly declined to decide this issue).²²⁰ The court also subtly reprimanded the FDA for not yet having published regulations.²²¹ However, almost another six years elapsed before the Regulations were finalized in 1993. Since the Regulations went into effect, the importance of *Genentech* has diminished. A similar case would now be decided under the Regulations.

218. See Arno et al., *supra* note 5, at 240; Janice M. Hogan, *Revamping the Orphan Drug Act: Potential Impact on the World Pharmaceutical Market*, 26 LAW & POL'Y INT'L BUS. 523, 533 (1995); Thomas, *supra* note 52, at 429-30.

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

220. See *id.* at 313.

221. See *id.*

The next case to discuss the Act was *Ortho Pharmaceutical Corp. v. Amgen, Inc.*²²² However, the Act was just a sidelight of what was essentially a contract case, and the court said nothing of interest about the Act.

Two recent cases are more interesting. The first is *Berlex Lab. v. Food and Drug Admin.*²²³ The case revolved around the FDA's approval of an interferon made by Biogen. Berlex claimed that the approval of Biogen's interferon violated its exclusivity in its own interferon, challenging the FDA's finding of clinical superiority.²²⁴ The Court held that Berlex had standing to sue the FDA,²²⁵ but held, in an opinion very deferential to the FDA's designation process, that the FDA had an adequate basis for its decision and so ruled against Berlex on the merits.²²⁶

The final case involving the Act is *Braintree Lab., Inc. v. Nephro-Tech, Inc.*,²²⁷ an unpublished decision from Kansas. Braintree had a drug with market exclusivity. Nephro-Tech sold a competing version of the same drug as a "dietary supplement" without FDA approval.²²⁸ Being unable to sue directly under the Food, Drug and Cosmetic Act (FDCA), Braintree submitted a set of patent, unfair competition, and common law tortious interference claims, as well as a claim for a violation of "property rights to seven years exclusivity under the Orphan Drug Act."²²⁹ The Court dismissed all of the claims as an impermissible attempt to evade the prohibition against an individual's suing directly under the FDCA.²³⁰ This case might give pause to any orphan drug exclusivity holder, who would thus seem to be unable to enforce its rights in court. However, Braintree probably should have instead first gone directly to the FDA and requested action. Then, if the FDA still refused to act, Braintree could have filed suit against the FDA, not directly against Nephro-Tech.

E. Biotechnology Protection

A surprising number of commentators have noted that the

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

223. *Berlex Lab., Inc. v. Food and Drug Admin.*, 942 F. Supp. 19 (D.D.C. 1996).

224. *See id.* at 23.

225. *See id.* at 24-25.

226. *See id.* at 23-24.

227. *Braintree Lab., Inc. v. Nephro-Tech, Inc.*, No. 96-2459-JWL, 1997 WL 94237 (D. Kan. Feb. 26, 1997).

228. *See id.* at *1.

229. *Id.* at *1-2.

230. *See id.* at *6-7.

Orphan Drug Act has, to some degree, become a sort of patent substitute for biotechnological inventions.²³¹ This practice has arisen from the uncertain state of patent protection for these inventions and the complexities of obtaining such protection. Preparation of an application for obtaining Orphan Drug Act exclusivity is much less onerous than prosecution of a patent for a protein or other biotechnology invention. Requests for orphan drug designation are straightforward, involving only the compilation and submission of information to the FDA, as provided in the Regulations.²³² Patent prosecution, on the other hand, requires a lengthy process of drafting and filing an application that explains the invention and then convincing the Patent and Trademark Office that the invention meets the statutory requirements for patentability.²³³ The absolute term of Orphan Drug Act's protection, seven years, is shorter than that of patent protection, twenty years.²³⁴ However, a biotechnology patent's term begins when the patent application is filed, and the time taken in patent prosecution and then clinical trials subtracts from the effective term. The term for orphan drug exclusivity, on the other hand, does not start until the drug is approved. The net effect is that the length of protection is about even, or may even favor exclusivity. On the other hand, orphan drug exclusivity does not have the versatility of a patent, and the uncertain status of biotechnology patents is slowly being resolved. However, when used for the limited purposes to which the Act is suited, orphan drug exclusivity can be a potent patent substitute.²³⁵

F. Other Applications of the Orphan Drug Act Concept

The Orphan Drug Act has been so successful at encouraging the

231. See Arno et al., *supra* note 5, at 236; Marlene E. Haffner, *Orphan Products—Ten Years Later and Then Some*, 49 FOOD & DRUG L.J. 593, 599-600 (1994); Joseph A. Levitt & John V. Kelsey, *The Orphan Drug Regulations and Related Issues*, 48 FOOD & DRUG L.J. 525, 531 (1993); Shulman et al., *supra* note 38, at 366; Jess G. Thoene, *Curing the Orphan Drug Act*, 251 SCIENCE, Mar. 8, 1991 at 1158. Even Congress has criticized this phenomenon. See S. REP. NO. 102-358, at *6-7 (1992) (1992 WL 193619) (report on S. 2060 Orphan Drug Amendments of 1992).

232. See 21 C.F.R. § 316.20 (1998).

233. See 35 U.S.C. §§ 101-103 (1994).

234. See 35 U.S.C. § 154(a)(2) (1994).

235. An entire article could be written on this subject, exploring how it came about and comparing the provisions of the two systems, particularly the scope of coverage. The FDA's proposed rules provide an excellent account of the various possibilities the FDA considered for defining the scope of protection, as contained in the "same drug" definitions. See Orphan Drug Regulations, 56 Fed. Reg. 3338, 3341-43 (1991) (proposed Jan. 29, 1991). For analysis from the patent side, see generally Merges & Nelson, *supra* note 134.

development of drugs for rare diseases that many people wish to replicate that success in other areas. For example: Congress has proposed to use the Act's concepts to help the development of drugs to treat addiction²³⁶ and the development of pesticides for use with minor crops.²³⁷ Geneticists have proposed a category of "orphan tests" for diagnosing people with rare diseases.²³⁸ Environmentalists have discussed using the concept to help facilitate the development of environmental technologies.²³⁹ Medical professionals have suggested applying the concepts to medical records systems²⁴⁰ and contraceptive technologies.²⁴¹ The Act has even influenced other countries to pass similar legislation.²⁴²

In a similar vein, some have suggested using the Orphan Drug Act as a model for legislation supporting the development of drugs that improve global health.²⁴³ However, the Act as it is written is already intended to do this. Some commentators have pointed to the fact that a disease might be rare in the U.S. but widespread elsewhere as a flaw in the Act, since the true affected population would then be greater than 200,000 and drug companies would thus have sufficient incentive to develop the drug even without the incentives of the Act.²⁴⁴ However, this is not a true flaw for two reasons. First, most of these large potential markets are in the developing world, where money for health care is scarce. A large potential market for a drug is irrelevant if those comprising that market lack the resources to purchase the drug. Second, Congress considered the issue of orphan

236. See S. REP. NO. 101-476, (1990) (1990 WL 201726) (report on the Drug and Alcohol Abuse Treatment and Prevention Improvement Act of 1990); see also 142 CONG. REC. S9742-9744 (daily ed. Sept. 3, 1996) (S. 2051 Pharmacotherapy Development Act).

237. See 136 CONG. REC. S5982 (daily ed. May 10, 1990) (statements of Sen. Graham referring to the program as "an orphan-drug program for agricultural chemicals").

238. See Leslie G. Biesecker, *Orphan Tests*, 5 CAMBRIDGE Q. HEALTHCARE ETHICS 300, 300 (1996).

239. See Natalie M. Derzko, *Using Intellectual Property Law and Regulatory Processes to Foster the Innovation and Diffusion of Environmental Technologies*, 20 HARV. ENVTL. L. REV. 3, 13-14 (1996).

240. See Stephen C. Schoenbaum & G. Octo Barnett, *Automated Ambulatory Medical Records Systems: An Orphan Technology*, 8 INT'L J. TECH. ASSESSMENT HEALTH CARE 598 (1992).

241. See Lisa Kaeser et al., *Contraceptives: On Their Own*, 8 INT'L J. TECH. ASSESSMENT HEALTH CARE 658 (1992).

242. See Mike Ward, *E.C.'s Orphan Drug Proposal*, 6 BIOCENTURY, Aug. 3, 1998 at A9 (1998); see generally Cavalier, *supra* note 122 (comparing the U.S., Japan and Europe).

243. See Patricia C. Kuszler, *Balancing the Barriers: Exploiting and Creating Incentives to Promote Development of New Tuberculosis Treatments*, 71 WASH. L. REV. 919, 965 (1996).

244. See Thomas, *supra* note 52, at 429; Buday, *supra* note 123, at 83.

drugs with large worldwide patient populations but small U.S. patient populations, and deliberately decided to limit the definition to the affected population in the U.S.²⁴⁵ Congress was quite willing to have the program serve as a mechanism to help develop treatments for diseases such as malaria that were prevalent in areas of the world that could not afford to develop such treatments, but that were still rare in the U.S. This aspect of the program has had its successes as well, developing products for treating malaria, leprosy, and African sleeping sickness.²⁴⁶

V. CONCLUSION

After some early fine tuning, and more recently the publication of the Regulations, the Orphan Drug Act has become a paragon of legislative virtue: it does exactly what it is supposed to do and it does it exceptionally well. It has brought forth treatments for rare diseases in unprecedented numbers and given a new level of hope to millions of people.

The Act has also been highly criticized. Most of the criticism stems from the existence of a few "blockbuster" drugs that have earned huge profits for their owners. These drugs, for the most part, arose from unique circumstances (AZT and pentamidine in response to the AIDS epidemic) or because of early mistakes in administering the Act (EPO submarketing). Most of these troubling drugs are now no longer protected, and, judging from the recent literature, few new ones have replaced them. Meanwhile, the Orphan Drug Act continues to deliver drugs for rare conditions.

As one long-term proponent of the Act observes, too much attention has been focused on the public costs of the Orphan Drug Act — and not enough on the public benefits.²⁴⁷ As more drugs become available, each person's risk of being diagnosed with an untreatable disease decreases. The costs of successfully treating many rare diseases, while high, are more than recouped in other health care savings and fuller societal participation of those with orphan diseases. "As just one example, patients with Parkinson's disease who can slow their disease progression with the orphan drug selegiline may save the

245. See H.R. REP. NO. 97-840, pt. 1, at 9 (1982), *reprinted in* 1982 U.S.C.C.A.N. 3577, 3581 (report on P.L. 97-414 Orphan Drug Act).

246. See Haffner, *supra* note 231, at 600.

247. See Asbury, *supra* note 159, at 897. The Act has also played a part in the rehabilitation of thalidomide, a drug long in disfavor. See Lisa Seachrist, *EntreMed Winds Orphan Drug Status For Thalidomide In KS*, 9 BIOWORLD TODAY, August 21, 1998 at 1 (1998).

public \$10 million per week by delaying the initiation of disability payments and by providing tax revenues while they continue to work."²⁴⁸

Despite this success, the discussions in Part III.A, *supra*, demonstrate that Congress frequently threatens to change the way the Orphan Drug Act works. These threats have led to a high level of uncertainty in the drug industry, and a certain leeriness about relying on the Act; some companies have even stopped filing for designation.²⁴⁹ Congress and the President need to decide once and for all what they want the Orphan Drug Act to be, then amend it that way and leave it alone. Or, better yet, just leave it alone now, as it is, and let it continue to do the job that it has done so well: getting drugs for rare diseases to market. Fortunately, this "reform" activity seems to have died down in the last few years; it should stay that way.

The situation of the Orphan Drug Act seems to lend itself to clichés — if it's not broken, don't fix it;²⁵⁰ don't throw the orphan out with the bathwater;²⁵¹ don't cut off your nose to spite your face.²⁵² A better conclusion is provided by David Kessler, then-Commissioner of the FDA, "[w]e must not tinker with this very successful act I don't think we know enough about these market forces to make certain any changes we make will not hurt."²⁵³

248. Asbury, *supra* note 159, at 897.

249. See Sanders, *supra* note 119, at 2624-25 (A "shadow of uncertainty" leading to "a chilling effect on research and development into orphan drugs is already being felt."); Rin-Laures & Janofsky, *supra* note 7, at 295; Clissold, *supra* note 154, at 141.

250. See Sanders, *supra* note 119, at 2625.

251. See Carey & Hamilton, *supra* note 102, at 38.

252. The author's contribution.

253. Sanders, *supra* note 119, at 2625.

