

THE ORPHAN DRUG ACT AND THE MYTH OF THE EXCLUSIVITY INCENTIVE

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For more than 20 years, the marketing exclusivity provision of the Orphan Drug Act has been hailed as a key component of the incentive for the United States' pharmaceutical industry to develop drugs for rare disorders; this is the Official Story of the ODA. In this paper, I argue that the Official Story is a myth. Rather, the real engine for the development of drugs to treat rare disorders is the patent system.

INTRODUCTION

Rare disorders are a serious health concern in the United States today, though their aggregate impact is rarely addressed in the public space. Congress has defined a "rare disease or condition"<sup>1</sup> as one that affects less than 200,000 people in the United States, or one that "affects more than 200,000 in the United States and for which there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from sales in the United States of such drug."<sup>2</sup> There are more than 6,000 such disorders, many of which are life-threatening or severely debilitating,<sup>3</sup> and they affect a total of more than 25 million Americans.<sup>4</sup> Through most of the 20<sup>th</sup> century, few drugs were developed to treat rare disorders because the small patient populations made it difficult for pharmaceutical

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<sup>1</sup> For the purposes of this paper, "rare disorder" will refer to both rare diseases and rare conditions.

<sup>2</sup> 21 U.S.C. § 360bb (2004).

<sup>3</sup> See Carol Rados, *Orphan Products: Hope for People With Rare Diseases*, FDA Consumer Mag., Nov.-Dec. 2003, at 11, at [http://www.fda.gov/fdac/features/2003/603\\_orphan.html](http://www.fda.gov/fdac/features/2003/603_orphan.html) (last visited Feb. 24, 2005).

<sup>4</sup> 21 U.S.C. § 360ee (2004).

companies to recoup their research and development (“R&D”) costs.<sup>5</sup> “Despite the urgent health need for these medicines, they came to be known as ‘orphans’ because companies were not interested in ‘adopting’ them.”<sup>6</sup>

To foster the development of orphan drugs, Congress passed the Orphan Drug Act (“ODA”) in 1983.<sup>7</sup> The ODA provides multiple incentives to drug developers, the most prominent of which is a seven-year marketing exclusivity period for drugs approved by the Food and Drug Administration (“FDA”) to treat a rare disorder. Congress has called the ODA a “tremendous success”<sup>8</sup> in fostering the development of orphan drugs. Most commentators agree, largely on the basis of the incentive provided by the marketing exclusivity provision. The 283 orphan drugs that have been FDA-approved since the passage of the Act<sup>9</sup> are the primary evidence that supports this claim; causation is assumed.

However, there is an independent force that has also been providing incentives to produce orphan drugs during the same period: the patent system. This paper argues that the ODA has not been the tremendous and independent success it is commonly claimed to be; rather, patent rights currently supply the most important incentive for developers of orphan drugs. Part I provides an introduction to the ODA, the “Official Story” of the ODA’s success, and the role of patent rights in the pharmaceutical industry.<sup>10</sup> Part II presents data indicating that the majority of orphan drugs approved over the years 2001-2003 were at least partially protected by patents and that the marketing exclusivity provision and other incentives of the ODA do not adequately explain the pharmaceutical industry’s activity in the realm of orphan drug development. Part III argues that developments in patent law, regulatory changes, and the growth of the pharmaceutical and biotech industries since the passage of the ODA provide a powerful alternative explanation for the subsequent development of orphan drugs. Part IV concludes that though the ODA is not the dominant force in orphan drug development, it nevertheless plays a significant role in the development of orphan drugs.

## I. THE OFFICIAL STORY OF THE ORPHAN DRUG ACT & THE PATENT PARALLEL

### A. *The Official Story of the ODA: A “Tremendous Success”*

#### 1. The Barriers to Orphan Drug Development

The Official Story of orphan drug development begins with a combination of market failure and regulatory disincentive. Developing a drug for *any* disorder is a long, expensive, and

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<sup>5</sup> See 21 U.S.C. § 360aa (2004).

<sup>6</sup> Rados, *supra* note 3, at 12.

<sup>7</sup> Orphan Drug Act, 21 U.S.C. §360aa *et seq* (2004).

<sup>8</sup> 21 U.S.C. § 360ee (2004).

<sup>9</sup> Food and Drug Administration Office of Orphan Products Development, Cumulative List of Orphan Products Designated and Approved, at <http://www.fda.gov/orphan/designat/list.htm> (last updated Jan. 18, 2006).

<sup>10</sup> For the purposes of this paper, “pharmaceutical industry” includes biotechnology companies that develop drugs unless otherwise specified.

risky endeavor. Drugs marketed in the United States must meet demanding safety and efficacy standards in order to be approved by the FDA.<sup>11</sup> In 2003, the average FDA approval time for a new small-molecule drug was 16.9 months; the average approval time for a new biologic was 34.7 months.<sup>12</sup> However, FDA approval is only part of a much longer R&D process: "it now takes an average of 10 to 15 years to bring a new medicine from the laboratory to the pharmacy."<sup>13</sup> Largely because of FDA approval requirements and the long development process, drug R&D costs are massive. Proving a concept for a new drug can exceed \$100 million,<sup>14</sup> and the average cost for an approved drug was \$802 million in 2003.<sup>15</sup> In the aggregate, the pharmaceutical industry spent over \$33.2 billion on R&D in 2003,<sup>16</sup> with only a small fraction of total costs being covered by public funding.<sup>17</sup>

FDA marketing approval is by no means a guarantee of market success; only three out of every ten marketed prescription drugs will produce revenues sufficient to recoup their R&D costs.<sup>18</sup> Yet, drug developers are willing to take the financial risk of developing drugs for prevalent conditions because a successful drug can be highly profitable.<sup>19</sup> Conversely, "when development costs cannot be recovered and profits are unlikely, drugs are not developed."<sup>20</sup>

The barriers to drug development are amplified in the context of rare disorders. Though rare disorders affect more than 25 million Americans,<sup>21</sup> any given disorder by definition affects just a small patient population, some as few as 100 people.<sup>22</sup> As a general matter, this both increases the risk for a rational drug developer and greatly reduces the potential return on investment from drug sales in a competitive market. Moreover, "[b]ecause [historically] ...the orphaned compounds generally were discovered during the course of research on a different

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<sup>11</sup> See Gary A. Pulsinelli, *The Orphan Drug Act: What's Right With It?*, 15 Computer & High Tech. L. J. 299, 303-4 (1999).

<sup>12</sup> Pharmaceutical Research and Manufacturers of America (PhRMA), *New Drug Approvals in 2003* 1 (Jan. 2004) at <http://www.phrma.org/newmedicines/resources/2004-01-22.123.pdf> (last visited Feb. 24, 2005).

<sup>13</sup> *Id.* at 16.

<sup>14</sup> Pharmaceutical Research and Manufacturers of America (PhRMA), *PhRMA 2003-2004 Annual Report* 4 (Oct. 2003), at <http://www.phrma.org/publications/publications//2003-11-20.870.pdf> (last visited Feb. 24, 2005).

<sup>15</sup> PhRMA, *New Drug Approvals in 2003*, *supra* note 12, at 1.

<sup>16</sup> *Id.*

<sup>17</sup> See Pharmaceutical Research and Manufacturers of America (PhRMA), *Pharmaceutical Industry Profile 2004* 5 (2004) (PhRMA Industry Profile 2004), at <http://www.phrma.org/publications/publications//2004-03-31.937.pdf> (last visited Feb. 24, 2005).

<sup>18</sup> *Id.* at 31.

<sup>19</sup> 1982 U.S.C.C.A.N. 3578.

<sup>20</sup> Patricia J. Kenney, *The Orphan Drug Act -- Is it a Barrier to Innovation? Does it Create Unintended Windfalls?* 43 Food Drug Cosm. L.J. 667 (1988).

<sup>21</sup> 21 U.S.C. §360ee (2004).

<sup>22</sup> Rados, *supra* note 3.

disease, their potential use in the treatment of a rare disease often was discussed in printed publications, the effect of which was to bar patentability under section 102 of the patent law.”<sup>23</sup> According to the Official Story, this combination of small market size and unpatentable drugs means that copycat drug makers that did not incur the R&D costs necessary to gain FDA marketing approval could easily underprice the initial drug developer.<sup>24</sup> Thus, without some other form of market protection, orphan drugs will not be produced.

“By the early 1980s ...the list of true orphan advancements ...was woefully short,”<sup>25</sup> and the industry was not focusing a substantial part of its primary research on rare disorders.<sup>26</sup> As of 1983, a total of only 38 orphan drugs had been developed.<sup>27</sup> Given the prohibitive costs and expertise necessary to bring these drugs to market, other institutions such as research hospitals and universities could do little to pick up the slack.<sup>28</sup> Faced with this serious public health problem, Congress took the first step in what would become a series of legislative actions by passing the Orphan Drug Act in 1983.

## 2. The Orphan Drug Act

The ODA in its present form contains four financial incentives and three non-financial incentives designed to encourage the development of orphan drugs. First, the ODA provides a seven-year period of marketing exclusivity for drugs approved by the FDA to treat a rare disorder.<sup>29</sup> This marketing exclusivity incentive is generally considered the most important and powerful incentive.<sup>30</sup> The purpose of marketing exclusivity is to assure a significant financial return by protecting a drug developer from competition by second-comers. This exclusivity is disorder-specific, which means that the FDA will not approve an application by another producer of the same drug for the same orphan disorder during the seven-year exclusivity period. However, the exclusivity provision does not prevent another producer of the same drug from gaining FDA approval for treating another condition.

As originally enacted in 1983, the ODA only applied to drugs for which no patent rights were available. However, for many reasons Congress quickly amended the Act to allow patented

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<sup>23</sup> David Duffield Rohde, *The Orphan Drug Act: An Engine of Innovation? At What Cost?* 55 Food & Drug L.J. 125, 127 n.12 (2000).

<sup>24</sup> Pulsinelli, *supra* note 11.

<sup>25</sup> John Henkel, *Orphan Products, New Hope for People with Rare Disorders*, FDA Consumer Spec. Rep. (Jan. 1995), at <http://www.fda.gov/fdac/special/newdrug/orphan.html> (last visited Feb. 24, 2005).

<sup>26</sup> See Rohde, *supra* note 23, at 127 n.11 (citing Donna Brown Grossman, *The Orphan Drug Act: Adoption or Foster Care*, 39 Food Drug Cosm. L.J. 128 (1984)).

<sup>27</sup> 21 U.S.C. §360ee (2004).

<sup>28</sup> Rados, *supra* note 22.

<sup>29</sup> 21 U.S.C. § 360cc (2004).

<sup>30</sup> See e.g. Office of Inspector General (OIG), *The Orphan Drug Act, Implementation and Impact* 8 (May 2001), at <http://oig.hhs.gov/oei/reports/oei-09-00-00380.pdf> (last visited Feb. 24, 2005).

and patentable drugs to gain orphan drug approval.<sup>31</sup> Most importantly, because pharmaceutical companies patent early in the drug development process,<sup>32</sup> patents on a drug for a rare disorder could expire before the seven-year exclusivity period ran out. Permitting patented drugs to receive an orphan designation allows the exclusivity period to function as a supplement to patent protection.<sup>33</sup> This preserves incentives to develop drugs for a given disorder, rather than forcing drug developers to make strategic judgments about how to protect their investment before they know what it does. This facet of the marketing exclusivity incentive has also been hailed as the “[p]rincipal economic benefit” of the ODA.<sup>34</sup> Second, while it was easy to determine which drugs were “unpatented,” it could be quite difficult to determine whether a drug was “unpatentable,” even with the assistance of the Patent and Trademark Office.<sup>35</sup> Third, the relaxed requirement is particularly helpful to biotech drug developers: at the time of the amendments, biotech drug developers did not believe that biotech drugs were well protected by patents,<sup>36</sup> and it can be difficult to seek protection for biotech drugs by patent.<sup>37</sup>

The second financial incentive the ODA provides is a 50% tax credit for qualified clinical testing expenses.<sup>38</sup> Qualified clinical testing is defined as clinical testing of the designated drug for the rare disorder that occurs between the dates of orphan designation and orphan approval. This tax credit is more favorable than a tax deduction because it can be claimed directly against taxes owed by the drug developer, rather than income to be taxed.<sup>39</sup> However, this tax credit is neither refundable nor recapturable.<sup>40</sup>

Third, the ODA established an Orphan Grant Program that provides direct financial assistance to orphan drug developers.<sup>41</sup> Congress has increased the level of funding for the Orphan Grant Program since the inception of the ODA, and it presently stands at \$25 million for

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<sup>31</sup> Orphan Drug Amendments of 1985, Pub. L. No. 99-91, 99 Stat. 387 (1985).

<sup>32</sup> Bruce N. Kuhlik, *The Assault on Pharmaceutical Intellectual Property*, 71 U. Chi. L. Rev. 93, 96 (2004).

<sup>33</sup> James L. Wheaton, *Generic Competition and Pharmaceutical Innovation: The Drug Price Competition and Patent Term Restoration Act of 1984*, 35 Cath. U. L. Rev. 433, 457 n.115 (1986).

<sup>34</sup> See James T. O'Reilly, Food and Drug Administration §13:14 (2d ed. 2004) (citing FDC Reports, *Exclusivity Extensions Are "Most Powerful" Orphan Drug Incentive*, 58 FDC Rep. (Pink Sheet) 4 (Sept. 16, 1996)).

<sup>35</sup> Pulsinelli, *supra* note 11.

<sup>36</sup> See Abbey S. Meyers, Symposium *Genetics and the Law: The Ethical, Legal, and Social Implications of Genetic Technology and Biomedical Ethics: "Intellectual Property at the Public-Private Divide:" A Response*, 3 U. Chi. L. Sch. Roundtable 581 (1996).

<sup>37</sup> Kathleen Kerr, *Diseases Without Clout: So-called 'Orphan' Illnesses Work Towards Recognition—And Funding for Drug Research*, Newsday.com (Mar. 30, 2004) (on file with the author).

<sup>38</sup> 26 U.S.C. § 45C (2004).

<sup>39</sup> Li-Hsien Rin-Laures and Diane Janofsky, Note, *Recent Developments Concerning the Orphan Drug Act*, 4 Harv. J.L. & Tech. 269, 277 (1991).

<sup>40</sup> *Id.* at 295.

<sup>41</sup> 21 U.S.C. § 360ee (2004).

each of the fiscal years 2004-2006.<sup>42</sup> The grants are currently parceled out in awards of \$150,000 for Phase I-III studies, and \$300,000 for continuing Phase II-III studies, for direct costs a year for up to three years.<sup>43</sup> This grant program applies to clinical studies on medical devices and medical foods as well as drugs.<sup>44</sup>

The ODA was amended in 1997 to provide a fourth financial incentive to drug developers in the form of an exemption from the FDA “user fees” for companies developing orphan drugs.<sup>45</sup> However, the exemption does not apply if the FDA prescription drug application includes an indication for other than a rare disorder. In 2001 these user fees were estimated at nearly \$500,000.<sup>46</sup>

In addition to the four financial incentives, the ODA currently includes three non-financial measures to encourage drug development. First, section 227 of the ODA created the Orphan Products Board – a top-down approach.<sup>47</sup> Comprising members of federal organizations including the Department of Health and Human Services, the FDA, the National Institutes of Health, and the Center for Disease Control, its functions are to evaluate implementation of the ODA and promote coordination among and between members of the public and private sectors. It is also active internationally.<sup>48</sup>

The other two non-financial incentives work from the bottom-up. The ODA contains a protocol assistance provision allowing orphan drug developers to request the direct assistance of the FDA in designing clinical trials to meet FDA approval requirements.<sup>49</sup> Protocol assistance is probably more useful to small drug developers that lack experience dealing with the unique problems presented by clinical trials involving small populations.<sup>50</sup>

Finally, the ODA “encourages” the use of “open protocols” under which patients who would not normally be able to participate in a clinical trial can also receive the drug during the clinical trial phase. Though the incentive provided by open protocols is small, it allows a drug developer to recover some costs from sales of the drug while simultaneously benefiting patients.<sup>51</sup>

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<sup>42</sup> *But see* Food and Drug Administration, FY2005 Request for Applications (RFA) for Orphan Grants (2004), at <http://www.fda.gov/orphan/grants/2005RFA.htm> (last visited Feb. 24, 2005) (stating that the estimated funding for FY2004 is \$13.2 million).

<sup>43</sup> *Id.*

<sup>44</sup> 21 U.S.C. § 360ee (2004).

<sup>45</sup> Food and Drug Administration Modernization Act of 1997, Pub. Law No. 105-115, 111 Stat. 2296 (1997).

<sup>46</sup> OIG, *supra* note 30, at 4.

<sup>47</sup> 42 U.S.C. § 236 (2004).

<sup>48</sup> *See* FDA Office of Orphan Products Development FY2001 Accomplishments, Biomedical Market Newsletter (Apr. 17, 2002).

<sup>49</sup> 21 U.S.C. § 360aa (2004).

<sup>50</sup> *See* Pulsinelli, *supra* note 11.

<sup>51</sup> *See id.*, at 312.

### 3. A “Tremendous Success”

In May 2001, the Office of Inspector General (“OIG”) reviewed the number of orphan designations and approvals since the act and found that the ODA motivates drug developers to develop orphan drugs.<sup>52</sup> When Congress amended the ODA in 2002, it stated in its findings that the ODA was a “tremendous success.”<sup>53</sup> As of this writing, there are 283 approved orphan drugs and more than 1160 active designations in the pipeline.<sup>54</sup> These drugs have a potential patient population of over 12 million,<sup>55</sup> and about 50% of the approved drugs are geared for use in children.<sup>56</sup> The OIG,<sup>57</sup> academics and practitioner commentators,<sup>58</sup> and representatives of patient groups<sup>59</sup> all agree that the correlated orphan drugs demonstrate the success of the ODA, and that this success is largely a result of the marketing exclusivity provision.

#### B. *The Patent Parallel in Pharmaceutical Innovation*

Lurking in the background of the Official Story is the patent system. The foundation of a patent is the right to exclude others from making, using, or selling the patented invention.<sup>60</sup> In the context of the pharmaceutical industry, patents can cover the product itself, the methods involved in making the product, and any possible method of using the product.<sup>61</sup>

Though the ODA is commonly seen as an alternative to the patent system, drug developers can choose either or both forms of protection. A patent, however, is potentially far broader than ODA marketing exclusivity, both substantively and temporally. An ODA exclusivity grant is roughly equivalent to a method of use patent for a particular substance, plus an injunction. As a stylized example, imagine a novel treatment for neck cancer: Chemical X. Once the first drug company gains orphan drug approval, no other company will also be able to gain FDA approval to market Chemical X to treat neck cancer for seven years. However, ODA protection is disorder-specific – another drug developer could get FDA approval to use Chemical X to treat ovarian cancer.

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<sup>52</sup> OIG, *supra* note 30, at 1.

<sup>53</sup> 21 U.S.C. 360ee (2004).

<sup>54</sup> See Food and Drug Administration Office of Orphan Products Development, *supra* note 9.

<sup>55</sup> See Rados, *supra* note 3.

<sup>56</sup> See Kerr, *supra* note 37.

<sup>57</sup> OIG, *supra* note 30, at 8.

<sup>58</sup> See, e.g., Robert A. Bohrer & John T. Prince, *A Tale of Two Proteins: The FDA's Uncertain Interpretation of the Orphan Drug Act*, 12 Harv. J.L. & Tech. 365, 380-81 (1999).

<sup>59</sup> See, e.g., Meyers, *supra* note 36.

<sup>60</sup> 35 U.S.C. § 271(a) (2004).

<sup>61</sup> See 35 U.S.C. § 101 (2004).

By contrast, a patentee could have the patent rights to Chemical X, the industrial process necessary to purify Chemical X, and the method of using Chemical X to treat specified conditions for which it is useful – or any combination of these rights. If the patent covers Chemical X itself, the patentee can prevent competitors from making or using Chemical X in almost any way. To further protect the actual subject matter of their patents, a patentee could sue to prevent third parties from providing materials whose only use would be in connection with Chemical X.<sup>62</sup> Because the grant of patent rights is not attached to any outside event like FDA approval, a patentee (or a non-patentee) could also acquire additional protective rights by filing for patents on new methods of production or new uses for Chemical X.<sup>63</sup> If a competitor infringed the drug developer's patents associated with Chemical X, remedies could include an injunction and damages for lost profits.<sup>64</sup>

Patents also provide greater temporal protection than the ODA exclusivity grant. The standard duration for a patent is 20 years from the date of the patent application.<sup>65</sup> In addition, the patentee has two tools to extend the duration of the patent grant.<sup>66</sup> A patentee can benefit from up to 5 years of extension under the Hatch-Waxman Act to recover time lost during the FDA approval process.<sup>67</sup> A patentee can also gain an extension of up to thirty months as part of an effort to ward off a generic competitor.<sup>68</sup> In theory, multiple patents with different application dates could provide some level of market protection for a given product for a much longer period than 20 years. However, in actual practice the long road of R&D and FDA approval shortens the effective lives of most drug patents. Accounting for the tools to extend the patent's duration, the average effective life of a patent is presently 11 to 12 years from the date of FDA marketing approval.<sup>69</sup>

Patents are critical to the drug development industry.<sup>70</sup> Indeed, the drug development industry is more reliant on patents than many other industries because of the risky development

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<sup>62</sup> See 35 U.S.C. § 271(c) (2004).

<sup>63</sup> See 35 U.S.C. § 271(a) (2004).

<sup>64</sup> See 35 U.S.C. §§ 283-284 (2004).

<sup>65</sup> 35 U.S.C. § 154 (2004).

<sup>66</sup> Terry G. Mahn, *Symposium Issue—Striking the Right Balance Between Innovation and Drug Price Competition: Understanding the Hatch-Waxman Act: The Hatch-Waxman Act During Patent Prosecution and Beyond*, 54 Food Drug L.J. 233, 234 (1999).

<sup>67</sup> The Drug Price Competition and Patent Term Restoration Act of 1984, Pub. Law No. 98-417 (1984).

<sup>68</sup> See 21 U.S.C. § 355 (2004).

<sup>69</sup> PhRMA, *Industry Profile 2004*, *supra* note 17, at 31.

<sup>70</sup> See Bohrer & Prince, *supra* note 58, at 378; Bruce N. Kuhlik, *Colloquium: Intellectual Property: The Assault on Intellectual Property*, 71 U. Chi. L. Rev. 93 (2004). See also Henry G. Grabowski, *Patents and New Product Development in the Pharmaceutical and Biotechnology Industries*, in *Science and Cents: Exploring the Economics of Biotechnology: Proceedings of a 2002 Conference Sponsored by the Federal Reserve Bank of Dallas* (John V. Duca and Mine K. Yücel, eds., 2003), <http://www.dallasfed.org/research/pubs/science/grabowski.pdf> (citing a study that found that pharmaceutical R&D managers place the highest importance on patents among factors important to R&D).

process.<sup>71</sup> Patents are a means of recouping the costs of approved drugs and enticing investors to provide the necessary capital for drug R&D. Because a patentee can prevent competitors from even experimenting on the patented substance, drug developers patent early.<sup>72</sup> Because the chances of success with a patented drug are remote – only 1 in 2500 patented drugs makes it to market – but the payouts are huge, drug developers patent often.<sup>73</sup>

The presence of patents in the background of orphan drug development thus raises an important question: which form of market protection are orphan drug developers actually relying upon?

## II. DEBUNKING THE MYTH

In this section, I present three lines of argument that counter the Official Story that the ODA has been the primary incentive for orphan drug development. First, the data I collected suggest that the marketing exclusivity provision is not providing the incentive: the high prevalence of patents among approved drugs strongly indicates that drug developers are relying on that system for market protection; the distribution of designated drugs across patient populations and the average patient population served are inconsistent with the assertion that the marketing exclusivity provision is the primary incentive; and the ratio of new orphan biologics to orphan new molecular entities is actually lower than for the industry as a whole, which is inconsistent with the assertion that the ODA favors biotech. Second, rapid approval of orphan drugs and the issue of off-label use cast additional doubt on the marketing exclusivity incentive. Third, the other financial incentives provided by the ODA are inadequate to explain orphan drug development because they are too small and unevenly distributed.

### A. *The Case Against Marketing Exclusivity*

#### 1. The Majority of Approved Orphan Drugs Have Some Patent Protection

As explained above, patents generally provide more extensive market protection than an ODA grant of marketing exclusivity. Thus, if the marketing exclusivity provision of the ODA is the *primary* incentive for orphan drug development, then the orphan drugs that are developed should either a) be generally without patent protection or b) have patent protection that will expire within seven years of ODA approval. In fact, neither appears to be the case.

Using information on orphan drug approvals available from the FDA as a starting point,<sup>74</sup> I searched for associated patent rights using the FDA's Online Orange Book.<sup>75</sup> Because

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<sup>71</sup> See Kuhlik, *supra* note 70, at 94-96.

<sup>72</sup> See Bohrer & Prince, *supra* note 58, at 377.

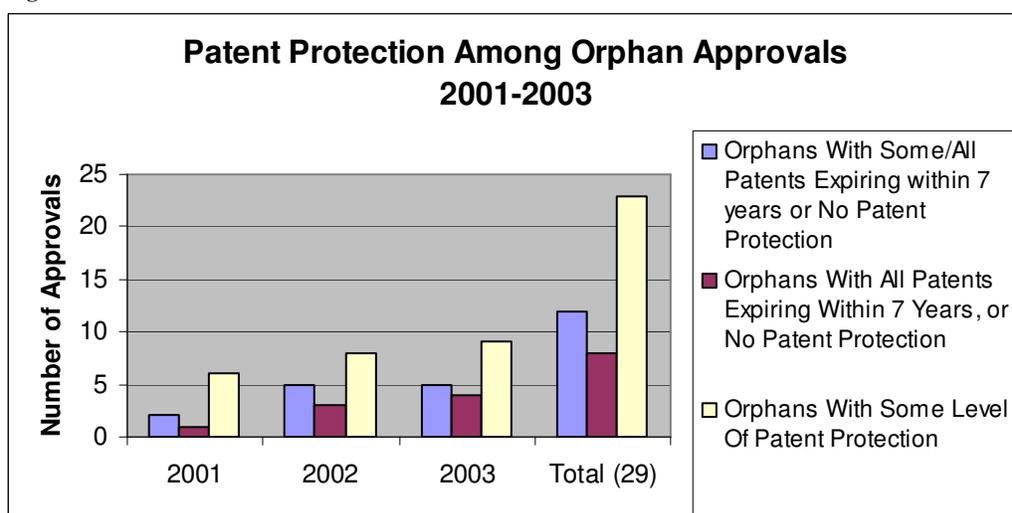
<sup>73</sup> See Mahn, *supra* note 66.

<sup>74</sup> Food and Drug Administration Office of Orphan Products Development, *supra* note 9.

<sup>75</sup> Food and Drug Administration Office of Pharmaceutical Science, Electronic Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, <http://www.fda.gov/cder/ob/default>.

information on some of the approved orphan drugs was not available from this source, I also searched the Federal Register and publicly available press releases on the internet.<sup>76</sup> I then compiled the number of orphan drug approvals with no associated patent protection, approvals with all associated patent protection set to expire within seven years of the approval date, and approvals with some associated patents set to expire within seven years of the approval date. The overall percentage with either no patent protection or some or all patents expiring within seven years provides the maximum number of circumstances where marketing exclusivity could be relevant. The percentage with all patents expiring within seven years, or no patent protection, provides the middle ground envisioned by the creators of the ODA. The percentage with associated patents provides a potential maximum for circumstances where marketing exclusivity would be irrelevant.<sup>77</sup>

Figure 1:



For the years 2001-2003<sup>78</sup>:

- Maximum relevance for the ODA: 41% of approvals were either not covered by patents, or some or all of the associated patent rights would expire before the seven year exclusivity period would run.
- The middle ground envisioned by the Official Story: 28% of the approvals were either without patent protection, or covered only by patents that would expire within the seven-year exclusivity period.

<sup>76</sup> Because my methodology would not necessarily reveal all of the patents associated with a given product, the data may underestimate the true extent of patent coverage.

<sup>77</sup> This percentage is not necessarily the remaining portion of all orphan drugs.

<sup>78</sup> The data for 2002 were adjusted to account for repeat occurrences of the same drug for different indications, on the theory that a drug developer reaps substantial R&D cost savings by pursuing approval for multiple indications simultaneously rather than separately.

- Maximum relevance of patents: 79% of approvals had some level of associated patent rights. Of these, 72% had patent rights that would expire after ODA marketing exclusivity ran out.

The high percentage of approvals with associated patents clearly demonstrates that patents are an important aspect of the orphan drug incentive. Moreover, the high prevalence of associated patents that will outlast the exclusivity grant strongly suggests that orphan drug developers are relying on patents for the *actual* protection of their approved orphan drugs. Now, it is important to note that the existence of an *associated* patent does not mean the patent is equivalent to the protection provided by orphan marketing exclusivity. That is, an orphan drug could be covered by 1000 patents, while the use of the drug to treat the specified orphan disorder remained unpatentable; a more detailed analysis is required to fully assess the actual coverage of the associated patents. Furthermore, this data does not prove what the drug developers' motives are *ex ante* because it does not show at what point the patents entered the R&D process.

However, there is reason to believe that the picture painted by this data is even stronger than the numbers suggest. First, the data above does not reflect which of the expiring patents may yet gain an extension of up to five years under Hatch-Waxman. Second, a patented drug developer does not necessarily need the patent equivalent of the ODA designation – i.e., a method of use patent for a particular indication – to gain market protection. If the drug developer has a patent on the product itself, the drug developer potentially gains a *de facto* monopoly over the methods of use of the product, for the simple reason that it is difficult to develop new uses for a product which you cannot legally make, use, or sell. This *de facto* monopoly can also exist to a lesser extent if the drug developer has a patent on the only known or only practicable method of producing the drug. An orphan drug with unclear or incomplete patent protection can also function as a deterrent to competition. In an industry already rife with risk and expense, a rational company may forgo R&D that could infringe a patent whose scope is unclear, or avoid domains in which a competitor has a substantial head start.

## 2. Orphan Drugs Are Not Being Produced For The Expected Population Groups

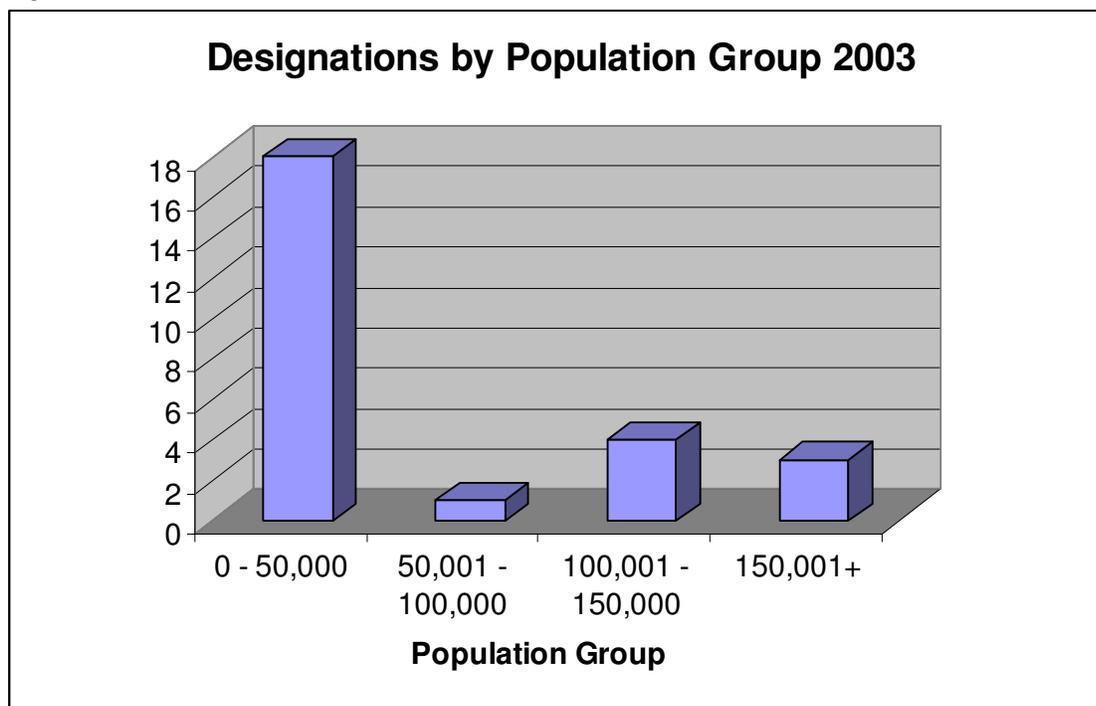
The population sizes of rare disorders for which companies have received orphan designations are a potentially powerful measure of the ODA's incentives. Because a company that receives an orphan drug designation still faces a long and uncertain approval process, this analysis provides a glimpse into the actual expectations of the drug developers. If the Official Story is true, and the seven-year marketing exclusivity provision is the primary incentive for developing an orphan drug, then in a vacuum one would expect to see both a high number of designations for the more prevalent rare diseases, as well as a high average population. Assuming that rational drug developers prefer larger markets, if marketing exclusivity were the only factor affecting incentives, the number of designations should at least increase steadily as the population size approaches 200,000.<sup>79</sup> Again, this does not appear to be the case.

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<sup>79</sup> One might even hypothesize that the distribution would be weighted towards the higher population groups, given that orphan designation is also available to population groups larger than 200,000 under some circumstances. See 21 U.S.C. § 360bb (2004).

I compiled population data on 26 products that received orphan designations in 2003<sup>80</sup> using a variety of publicly available sources and proprietary databases.<sup>81</sup> I then found an average population size for the group, and separated the population sizes into large subgroups for comparison.

Figure 2:

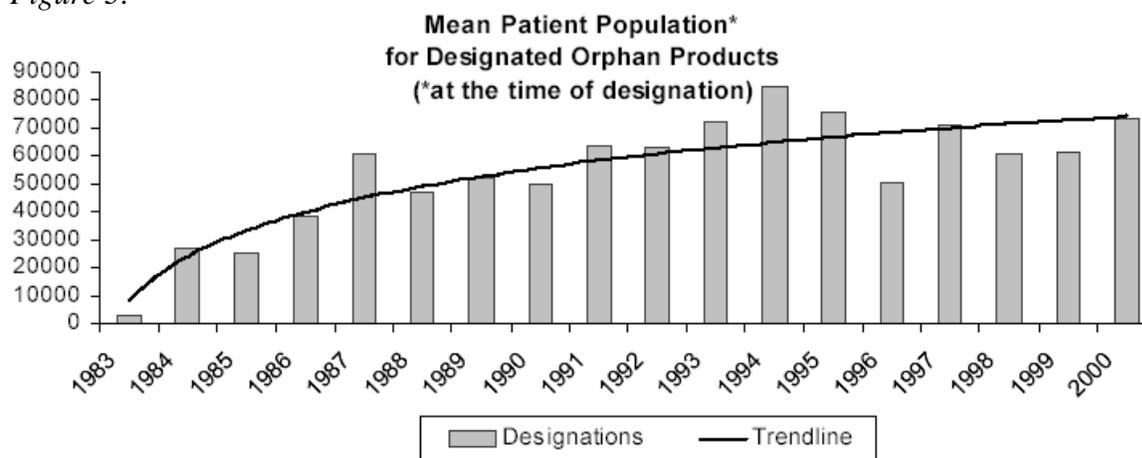


Of 26 designations, 18 (69%) were for populations of 50,000 or less. Of the designations in the 0-50,000 category, 14 (54% of the total) were in the 20,000-50,000 range. The overall average population was 67,200. This average is consistent with the findings of the OIG, which analyzed the data submitted to the FDA for designations in the year 2000 and found an average prevalence of 73,000.<sup>82</sup>

<sup>80</sup> I selected the first 29 of 95 entries for 2003 by date of appearance, and found reasonable data on 26 of the designated disorders. I assumed that the date of designation within the year 2003 has no significant relation to the incentives for seeking the designation.

<sup>81</sup> The population data are problematic, at best. Estimates of population sizes for rare disorders vary significantly across sources. In some cases, I estimated population sizes based on annual incidence and mortality rates. Thus, I draw conclusions from large population categories, rather than data points, as this builds in skepticism about the accuracy of the data. It is also important to note that the population demographics of rare diseases as a whole have not been well studied, i.e. the distribution of rare disorder population sizes may not be flat or linear.

<sup>82</sup> OIG, *supra* note 30, at 11. The OIG also noted the problematic nature of population estimates for rare disorders: "Documenting patient prevalence for some very rare conditions may be a challenge. The Office of Orphan Products faces similar challenges when it attempts to verify the prevalence data that sponsors provide." *Id.* at 12.

Figure 3:<sup>83</sup>

These numbers are perhaps good news for people with rare diseases, because they indicate that orphan drug development is not disproportionately serving the highest population groups. However, these numbers are bad news for the Official Story of the marketing exclusivity incentive. Even when viewed in the light most favorable to the ODA, because the majority of designations are unevenly distributed, this data shows that the causal link between population size and R&D choices is not adequately explained by marketing exclusivity alone.

### 3. The ODA Does Not Favor the Approval of New Orphan Biologics Compared to the Pharmaceutical Industry Generally

One of the commonly cited explanations for the incentive provided by the ODA's marketing exclusivity provision involves the particular concerns faced by the biotechnology industry. On the patent front, biotechnology companies historically have faced uncertain patent protection<sup>84</sup> and difficulty patenting biotech discoveries.<sup>85</sup> Regarding the industry generally, the OIG concluded that the ODA has been "particularly helpful" to the biotech industry because "the prospect of marketing exclusivity under the [ODA] helps biotechnology companies attract venture capital...."<sup>86</sup> If this assessment of the ODA's incentives is correct, it should be reflected in the proportion of biologics that are approved for orphan designations relative to the industry as a whole. Specifically, if marketing exclusivity under the ODA favors biotech, one would expect

<sup>83</sup> *Id.* at 12.

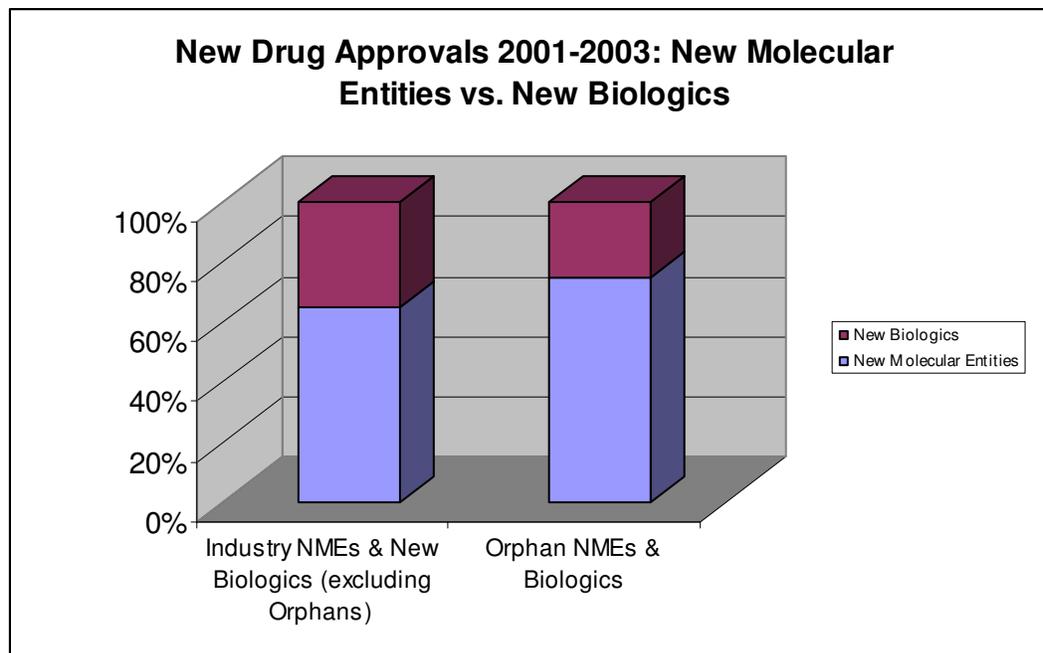
<sup>84</sup> *See Meyers, supra* note 36.

<sup>85</sup> Kathleen Kerr, *supra* note 37.

<sup>86</sup> OIG, *supra* note 30, at 8.

to see a larger ratio of new biologics to new molecular entities (NMEs)<sup>87</sup> among orphan drug approvals than among non-orphan drug approvals.<sup>88</sup> Again, this is not the case.

Figure 4:



Based on reports published by the Pharmaceutical Research and Manufacturers of America (PhRMA) on new drug approvals for the years 2001-2003,<sup>89</sup> I found that new biologics comprised 35% of all new drug approvals excluding orphans. New biologics comprised 25% of all new orphan approvals over the same period.

#### 4. Rapid Approval & Off-Label Use

There are two additional reasons to doubt the Official Story of the marketing exclusivity incentive: the speed of orphan drug approval and off-label concerns. Between 1998 and 2001, “[f]or standard rated drugs, the development time for orphans was nearly a year shorter than for non-orphans, while for priority rated products, orphan development time was only three months

<sup>87</sup> “The Food and Drug Administration classifies a drug as an NME if the active ingredient has never been previously marketed in the United States for use in a drug product either as a single ingredient or part of a combination.” Pharmaceutical Research and Manufacturers of America (PhRMA), *New Drug Approvals in 2002* (Jan. 2003), <http://www.phrma.org/newmedicines/resources/2003-01-30.102.pdf> (last visited Feb. 24, 2005).

<sup>88</sup> This analysis excludes new drugs that are not NMEs and new indications for previously approved medicines.

<sup>89</sup> See generally Pharmaceutical Research and Manufacturers of America (PhRMA), *New Drug Approvals in 2003*, *supra* note 12; Pharmaceutical Research and Manufacturers of America (PhRMA), *New Drug Approvals in 2002*, *supra* note 87; Pharmaceutical Research and Manufacturers of America (PhRMA), *New Drug Approvals in 2001* (Jan. 2002), at <http://www.phrma.org/newmedicines/resources/2002-01-25.46.pdf> (last visited Feb. 24, 2005).

shorter.”<sup>90</sup> Simply put, the faster orphan products are approved, the more valuable associated patent rights become.

Once a drug is approved for sale, it is possible for physicians to prescribe the drug “off-label” for disorders other than that for which it was tested. In the absence of patents, significant off-label potential is actually a deterrent to seeking ODA approval.<sup>91</sup> Because ODA exclusivity is disorder-specific, a drug developer will not be able to prevent a competitor from gaining FDA approval for the off-label use. Once competition arises in a substantial secondary market, the exclusivity in the first market may be destroyed by off-label prescribing in the primary market.<sup>92</sup> However, in an orphan drug development landscape, where patents are prevalent, off-label use once again becomes an incentive to develop orphan drugs. Because a product patentee (and, to a lesser extent, a method of production patentee) can prevent competitors from developing other uses for the product, the patentee can retain the value of the sales for both the approved and the off-label uses. Fundamentally, this incentive stems from the patent system.

### B. *Neither by Tax, by Grant, nor by User Fee*

Given the litany of reasons to doubt the incentive provided by the ODA’s marketing exclusivity provision, the question becomes: are ODA’s other financial incentives actually providing the real incentive for orphan drug development? The answer: probably not.

#### 1. The Tax Credit is Inadequate

The ODA’s 50% tax credit for qualified clinical trial costs<sup>93</sup> potentially represents large sums for approved drugs. A recent study of 25 biopharmaceutical firms found

[T]he average cost of Phase I trials is \$5,500 per patient. Sponsors spend about \$6,500 per patient in Phase II trials and more than \$7,600 per patient for Phase III studies. And considering that each additional day a drug spends in clinical development is estimated to cost from \$600,000 for niche drugs up to \$8 million for a blockbuster, the additional time spent in trials results in staggering losses for pharmaceutical companies.<sup>94</sup>

Yet, there are two reasons to doubt the effectiveness of the tax credit, and thus to doubt that it is the true source of the orphan drug incentive. First, the tax credit does not cover pre-clinical

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<sup>90</sup> Tufts Center for the Study of Drug Development, 4 Impact Report, Issue 3 (May/June 2002) (summary), at [http://csdd.tufts.edu/\\_documents/www/Doc\\_309\\_30\\_893.pdf](http://csdd.tufts.edu/_documents/www/Doc_309_30_893.pdf).

<sup>91</sup> See Pulsinelli, *supra* note 11, at 339-40.

<sup>92</sup> *Id.* at 340.

<sup>93</sup> 26 U.S.C. § 45C (2004).

<sup>94</sup> Lisa Roner, *Accelerating Clinical Trials: Strategies to Improve Efficiency*, Eyeforpharma Briefing (June 7, 2004), at <http://www.eyeforpharma.com/index.asp?nli=o&g-p&nld=6/7/2004&news=42041>.

testing,<sup>95</sup> which represents 33.8% of total pharmaceutical spending on drug development.<sup>96</sup> Second, not all drug developers qualify. Because the tax credit is neither refundable nor recapturable, it is only of use if a drug developer has sufficient income in a given year to rise above the minimum tax; a drug developer must also meet the “carrying on business” requirement for the tax credit.<sup>97</sup> Though the tax credit may be valuable to a large pharmaceutical company, many biopharmaceutical drug developers are ineligible because they have either have no sales, a small income, and/or cannot meet the “carrying on a business” requirement.<sup>98</sup> The upshot for the Official Story: the tax credit is unevenly distributed in the pharmaceutical industry, and it is not clear that the tax credit is a large enough factor in drug profitability even for the drug developers that do qualify.

## 2. Grants and User Fees Are Small

The grant program and user fees exemption similarly fail to provide adequate financial incentives to explain orphan drug development. The current maximum grant of \$300,000 for three years<sup>99</sup> and an extra \$500,000<sup>100</sup> for a user fee exemption are paltry sums relative to the \$802 million price tag for developing a typical drug.<sup>101</sup> Both financial incentives have limits. The amount of grant funding available is limited by the statute to \$25 million for all applicants.<sup>102</sup> The user fee exemption is limited because applicants that also pursue a non-orphan indication for the product may not qualify.<sup>103</sup> Like the tax credit, these financial incentives are too small and unevenly distributed to explain the development of orphan drugs.

### III. AN ALTERNATIVE EXPLANATION FOR THE DEVELOPMENT OF ORPHAN DRUGS

Understanding the development of orphan drugs since the passage of the ODA requires consideration of the confluence of two factors omitted from the Official Story: developments in patent law and the growth of the pharmaceutical and biopharmaceutical industries. These two

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<sup>95</sup> Rin-Laures & Janofsky, *supra* note 39, at 295.

<sup>96</sup> PhRMA Industry Profile 2004, *supra* note 17, at 43.

<sup>97</sup> Rin-Laures & Janofsky, *supra* note 39, at 295.

<sup>98</sup> *Id.*

<sup>99</sup> Food and Drug Administration, FY2005 Request for Applications (RFA) for Orphan Grants, *supra* note 42.

<sup>100</sup> OIG, *supra* note 30, at 4.

<sup>101</sup> PhRMA, New Drug Approvals in 2003, *supra* note 12, at 1.

<sup>102</sup> 21 U.S.C. § 360ee (2004). *But see* Food and Drug Administration, FY2005 Request for Applications (RFA) for Orphan Grants, *supra* note 42 (stating that the estimated funding for FY2004 is \$13.2 million).

<sup>103</sup> *See* 21 U.S.C. § 379h (2004).

factors may in fact furnish a complete understanding of orphan drug development during that period.

### A. *Developments in Patent Law*

#### 1. Patentable Biotech

The most important contribution to orphan drug development may be the recent advent of patentable biotech. In 1980, three years prior to the passage of the ODA, the history of patent law took a sharp turn when the Supreme Court held that a live, man-made microorganism was patentable subject matter.<sup>104</sup> The Court reasoned that because the engineered bacteria did not exist in nature, it fit the definitions of “manufacture” and “compositions of matter” under §101 of the Patent Act.<sup>105</sup> This decision paved the way for a torrent of biotech patents, including patents on human genes<sup>106</sup> and patents on whole animals.<sup>107</sup> Patentable biotech in turn set the stage for the development of the biopharmaceutical industry.

#### 2. The Court of Appeals for the Federal Circuit (CAFC)

Another critical part of the orphan drug explanation may be the advent of the CAFC. From the beginning of the 20<sup>th</sup> century through the 1970’s, the strength of patent protection generally declined in the U.S.<sup>108</sup> A combination of strong antitrust enforcement, hostility to patents in the Federal Courts, and inconsistent rulings across the circuits destabilized the system.<sup>109</sup> In 1982, just nine months before the passage of the ODA, Congress responded to calls for reform by creating the CAFC, a centralized appellate court for patent cases.<sup>110</sup> The CAFC immediately took a pro-patent stance, and has significantly broadened the rights of patent-holders in several ways since its inception: the CAFC has strongly favored patentees by affirming holdings of patent infringement; it has increased the strength of the injunction and damage remedies available to patentees; and the CAFC has helped to expand the scope of patentable subject matter.<sup>111</sup> Applied to the drug development industry, these changes brought

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<sup>104</sup> See generally *Diamond v. Chakrabarty*, 447 U.S. 303 (1980).

<sup>105</sup> *Id.* at 308-309.

<sup>106</sup> *E.g.*, U.S. Pat. No. 5,693,473 (filed June 7, 1995).

<sup>107</sup> *E.g.*, U.S. Pat. No. 4,736,866 (filed June 22, 1984) (the “Oncomouse”).

<sup>108</sup> Adam B. Jaffe & Josh Lerner, *Innovation and Its Discontents: How Our Broken Patent System is Damaging Innovation and Progress, and What to Do about It* 97-100 (Princeton University Press 2004).

<sup>109</sup> *Id.*

<sup>110</sup> *Id.* at 100.

<sup>111</sup> *Id.* at 101-19.

by the CAFC have undoubtedly increased the role of the patent system as an incentive to produce orphan drugs.

### 3. Hatch-Waxman & the Prescription Drug User Fees Act (PDUFA)

The role of the patent incentive has also been increased by regulatory reforms that have increased the effective life of patents. Such reforms are actually a two-pronged attack on the Official Story of the ODA, because a longer effective life both increases the value of a patent, and decreases the chance the ODA exclusivity will be relevant.

The most prominent of these reforms is the Hatch-Waxman Act (Hatch-Waxman) of 1984, which provides patent term extensions of up to five years for drug developers to allow them to regain time lost during the approval process.<sup>112</sup>

Second, the Prescription Drug User Fees Act (“PDUFA”) of 1992 requires drug developers seeking FDA approval to pay “user fees” to the FDA.<sup>113</sup> The FDA agreed to use these funds to hire more reviewers to speed up the approval process.<sup>114</sup> Though not typically viewed as a patent reform measure, the PDUFA has been instrumental in increasing the effective life of patents because of its success in decreasing FDA approval time. Since the passage of the act, average drug approval times have dropped from 30 months to 18 months overall.<sup>115</sup>

### 4. The Modern Patent

The modern patent is far stronger than the ODA marketing exclusivity right. As discussed in part I-B and part II-A, *supra*, patents have a wider scope than the disorder-specific ODA exclusivity provision. In the early 80’s biotech patents were born; since then the CAFC has increased the security of all patentees’ rights. Both Hatch-Waxman and the PDUFA have kept the duration of the patent right in tune with the times. The typical drug patent now has an effective life of 11-12 years,<sup>116</sup> far longer than the seven years provided by the ODA exclusivity provision. In fact, relatively few biopharmaceutical patents have expired to date.<sup>117</sup>

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<sup>112</sup> The Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417.

<sup>113</sup> 21 U.S.C. § 379h (2004).

<sup>114</sup> Tufts Center for the Study of Drug Development, Outlook 2004, glossary, *available at* <http://csdd.tufts.edu/InfoServices/OutlookPDFs/Outlook2004.pdf> (last visited Feb. 24, 2005).

<sup>115</sup> PhRMA, 2003-2004 Annual Report, *supra* note 14, at 11.

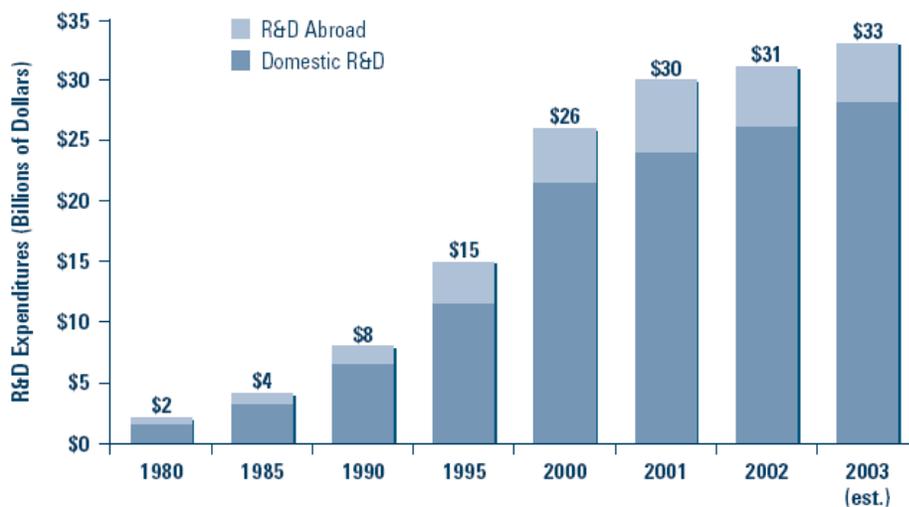
<sup>116</sup> PhRMA Industry Profile 2004, *supra* note 17, at 31.

<sup>117</sup> Grabowski, *supra* note 70, at 94.

## B. Industry Growth

Looking at history of drug development from 40,000 feet, industry growth since the 1980's has been phenomenal. R&D spending in the pharmaceutical industry as a whole has since the 1980's increased from \$2 billion in 1980, to over \$33 billion in 2003.<sup>118</sup> This growth in the U.S. is also part of a larger trend worldwide.<sup>119</sup> Naturally, as the pharmaceutical industry grows, the nation's medicine chest grows as well.

Figure 5:<sup>120</sup>



The biotech and biopharmaceutical industries were born in the 1980's and have come to play a powerful role in the drug development industry. The first biotech drug, synthetic human insulin, was only approved by the FDA in 1982.<sup>121</sup> The field of recombinant technology opened with the FDA approval of the first biotech-derived interferon drugs in 1986.<sup>122</sup> In 1997, the FDA approved the first monoclonal antibody drug to treat cancer.<sup>123</sup> The 1990's also saw two milestones in the understanding of DNA: the Human Genome Project began in 1990 and finished sequencing the first human chromosome in 1999.<sup>124</sup> "By 1994, only twenty-nine new biologic entities had been introduced into the U.S. market, but this number has increased dramatically

<sup>118</sup> PhRMA Industry Profile 2004, *supra* note 17, at 7.

<sup>119</sup> *See id.* at 4-5.

<sup>120</sup> *Id.* at 7.

<sup>121</sup> PhRMA, 2003-2004 Annual Report, *supra* note 14, at 11.

<sup>122</sup> *Id.* at 16.

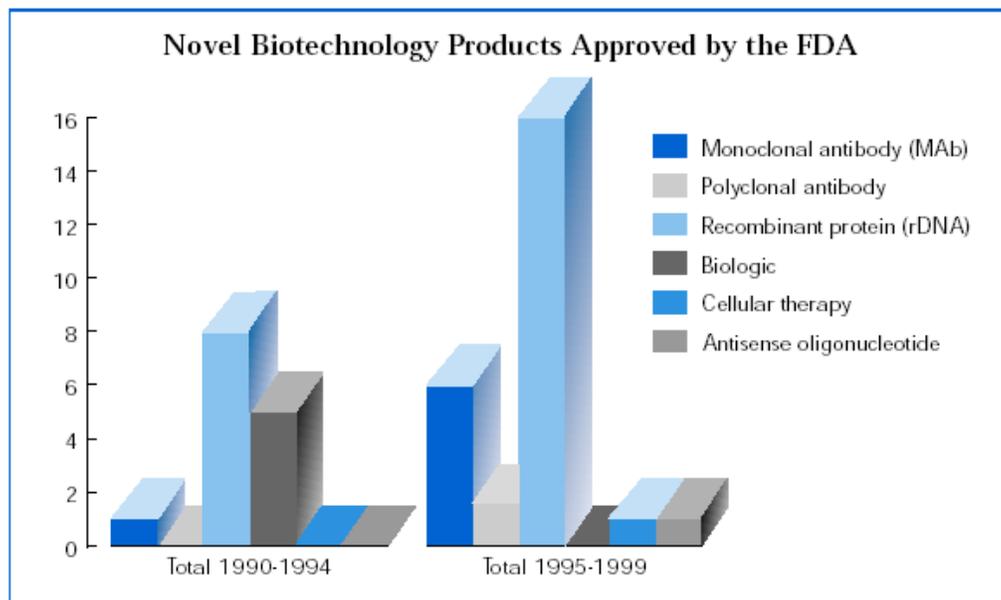
<sup>123</sup> *Id.* at 24.

<sup>124</sup> *Id.* at 20, 25.

since then. In this regard, forty-one new biological introductions occurred between 1995 and 2001.”<sup>125</sup>

Figure 6:<sup>126</sup>

**NEW BIOTECH PRODUCTS NEARLY DOUBLED DURING THE 1990s**



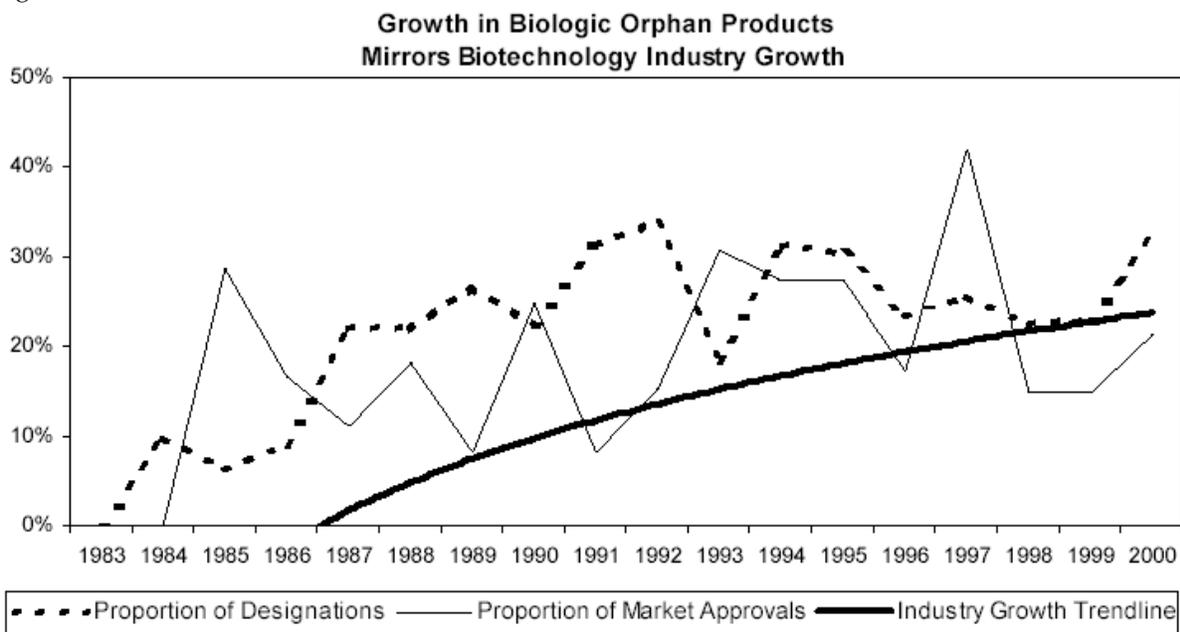
The implication: if the ODA has played a significant role in increasing the existing incentives to produce orphan drugs, the rate of orphan drugs development should exceed the rate of industry growth.<sup>127</sup> Instead, the study conducted by the OIG shows that the growth in biologic orphan products mirrors biotech industry growth.<sup>128</sup>

<sup>125</sup> Grabowski, *supra* note 70 at 92.

<sup>126</sup> Tufts Center Outlook 2004, *supra* note 114, at 4.

<sup>127</sup> It is also plausible that historically the ODA has provided an incentive, though only sufficient to keep the rate of orphan product development in line with industry growth. Further research is necessary to assess this possibility.

<sup>128</sup> OIG, *supra* note 30, at 8.

Figure 7:<sup>129</sup>

#### IV. CONCLUSION: A TEMPERED PERSPECTIVE

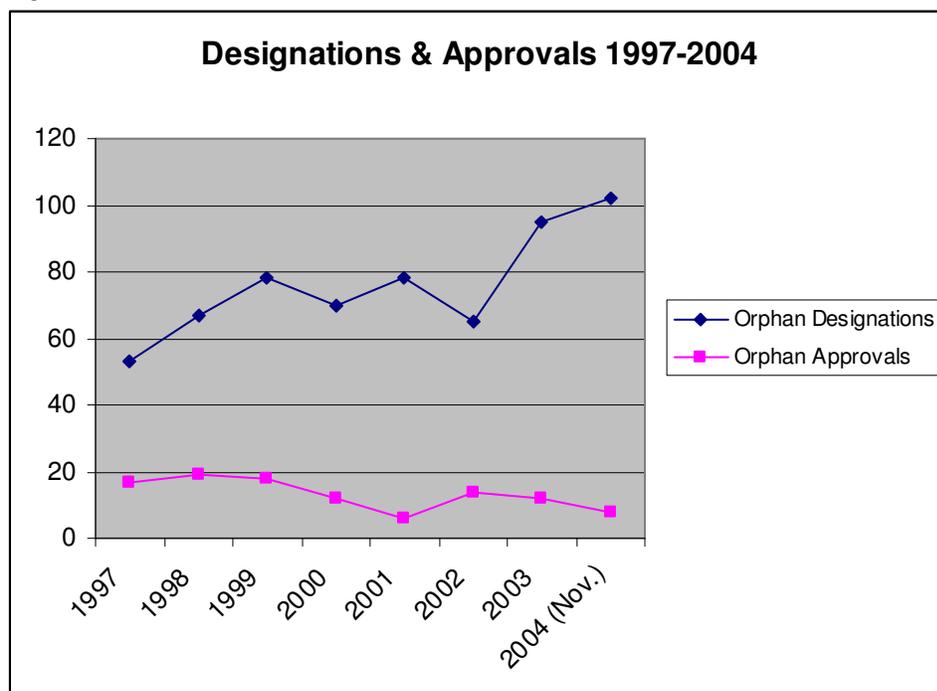
Two conclusions can be drawn from the arguments against the Official Story of the ODA. It may be that the ODA has simply been superfluous this whole time. The true engine of orphan drug development has been the patent system, in combination with massive industry growth. There are a high number of orphan drug designations because the two systems are not mutually exclusive: logically, a drugs developer should get an ODA designation regardless of its true incentives *ex ante*.

However, a more nuanced analysis of the ODA supports the theory that, though the ODA may not be the dominant incentive for orphan drugs, it remains a substantial factor. First, the sheer number of orphan designations – 1160 as yet unapproved by the FDA,<sup>130</sup> and counting – indicates that the drug development industry attends to the ODA in a systematic fashion. Indeed, the number of designations per year has been increasing over the last decade.

<sup>129</sup> *Id.*

<sup>130</sup> FDA Office of Orphan Products Development, *supra* note 9.

Figure 8:



Second, the aggregate financial and non-financial incentives provided by the ODA probably have a non-negligible effect on *ex ante* decision-making. The tax credit may be a significant – though perhaps not dispositive – consideration for established drug development companies with substantial revenue. For smaller drug companies, although protocol assistance, grants, and user fee exemptions may only represent a small contribution to the overall process of bringing a drug to market, they may represent an important contribution to early-stage drug development.

Finally, at some level the ODA is clearly serving its ideal constituency: developers of unpatentable drugs, and drugs for which patent protection will expire within seven years of approval. In these 28% of cases, though a minority, the ODA likely provides the market protection necessary for developers to risk orphan drug development. For the patented remainder, the ODA still has theoretical value as a form of insurance. If patents are weak or invalidated through litigation, ODA exclusivity held in reserve becomes an extremely valuable asset.

The inaccuracy of the Official Story should not be the final chapter of the ODA. Regardless of the source of the development incentive, orphan drugs help relieve the suffering of millions of people with rare disorders. Orphan drugs save lives. The task now should be to expand the incentives provided by the ODA and turn the myth of “tremendous success” into a reality.