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ADOPTING PHARMACOGENOMICS AND PARENTING REPURPOSED MOLECULES UNDER THE  
ORPHAN DRUG ACT: A COST DILEMMA?

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## ABSTRACT

The business model under which the pharmaceutical industry has operated in the recent past has become untenable. The era that has seen a consistent pipeline of blockbuster medicines for common chronic diseases is waning. New paradigms for more efficient and more economical drug development are being sought and implemented. Recent growth both in the repurposing of existing drugs and in the orphan product market has signaled the new hope for success and profit. New technology and the promise of personalized medicine augment the sense of optimism in this time of complementary transition in the wider healthcare industry. Yet, are the new paradigms sustainable within the framework of the Orphan Drug Act as implemented today? What is the cost of rare disease and orphan product development to the relevant stakeholders: government, private payers, patients and families, caregivers, research universities, biotechnology firms, and pharmaceutical companies? This article considers the perpetual debate: what is the appropriate balance between access and innovation, specifically in the context of incentivizing therapies for rare disease?

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## ADOPTING PHARMACOGENOMICS AND PARENTING REPURPOSED MOLECULES UNDER THE ORPHAN DRUG ACT: A COST DILEMMA?

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### I. HEALTHCARE AND PRESCRIPTION DRUG OVERVIEW

A macroeconomic view of healthcare costs in the United States reveals an unsustainable trajectory. Despite the recent slowdown in the growth of healthcare spending, it is well documented that the cost curve of healthcare has trended upward in the U.S., which spends approximately 17.9% of gross domestic product (“GDP”) on healthcare annually.<sup>1</sup> U.S. healthcare spending topped \$2.8 trillion in 2012—\$8,915 per person—with a growth rate of 3.7%.<sup>2</sup> The per capita expenditure exceeds that of Norway, the second highest, by more than \$2,500.<sup>3</sup> Furthermore, there is no evidence that the added investment improves health outcomes.<sup>4</sup>

The cost of prescription drugs mimics this general trend, although still only 11% of total healthcare spending in the U.S.<sup>5</sup> Of note, the U.S., unlike many other countries, has a private pharmaceutical market with no caps on the pricing structure.<sup>6</sup> Retail prescription drug

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\* © David C. Babaian 2014. David C. Babaian received his J.D. from The John Marshall Law School in 2005. After serving as a judicial clerk in the U.S. Court of Appeals for the Fifth Circuit and, thereafter, adjudicating disability claims with the U.S. Department of Veterans Affairs, he recently completed the LL.M. program in health law at the University of Washington, while working at Quorum Review IRB. Though there are numerous mentors and colleagues owed a debt of gratitude, the author would especially like to thank Mary and Richard Babaian and Dawn Stanek for their constant support and insight.

<sup>1</sup> Mark B. McClellan, *Bending the Cost Curve in Health Care the Right Way—Through Better, More Person-Centered Care*, BROOKINGS (May 9, 2013, 1:54 P.M.), <http://www.brookings.edu/blogs/up-front/posts/2013/05/09-bending-health-care-cost-curve-mcclellan>.

<sup>2</sup> *National Health Expenditures 2012 Highlights*, CTRS. FOR MEDICARE & MEDICAID SERVS. 1, <http://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/NationalHealthExpendData/downloads/highlights.pdf> (last visited Apr. 13, 2014) [hereinafter *CMS 2012 Highlights*].

<sup>3</sup> Anne K. Lindahl, *The Norwegian Health Care System, 2012*, in INTERNATIONAL PROFILES OF HEALTH CARE SYSTEMS, 2012 87 (Sarah Thomson et al. eds., 2012), available at [http://www.commonwealthfund.org/~media/Files/Publications/Fund%20Report/2012/Nov/1645\\_Squires\\_intl\\_profiles\\_hlt\\_care\\_systems\\_2012.pdf](http://www.commonwealthfund.org/~media/Files/Publications/Fund%20Report/2012/Nov/1645_Squires_intl_profiles_hlt_care_systems_2012.pdf); *Snapshots: Health Care Spending in the United States & Selected OECD Countries*, HENRY J. KAISER FAMILY FOUND. (Apr. 12, 2011), <http://kff.org/health-costs/issue-brief/snapshots-health-care-spending-in-the-united-states-selected-oecd-countries/> [hereinafter *Snapshots*, KAISER].

<sup>4</sup> *Snapshots*, Kaiser, *supra* note 3.

<sup>5</sup> *The Medicare Part D Prescription Drug Benefit*, HENRY J. KAISER FAMILY FOUND. (Nov. 19, 2013), <http://kff.org/medicare/fact-sheet/the-medicare-prescription-drug-benefit-fact-sheet/>.

<sup>6</sup> See generally, Neeraj Sood et al., *The Effect of Regulation on Pharmaceutical Revenues: Experience in Nineteen Countries*, 28 HEALTH AFFAIRS w125, w125, w126 (2009) (citing an

spending increased 0.4% to \$263.3 billion in 2012, following a 2.5% increase in 2011.<sup>7</sup> The acceleration was partly due to both faster growth in prescription drug prices, particularly for brand-name and specialty drugs, and increased spending on new brands.<sup>8</sup> Still, the growth in spending on retail prescription drugs has slowed significantly over the past decade, falling from 11.6% in 2000 to 1.2% in 2010.<sup>9</sup> This deceleration is attributable, in part, to the increasing prevalence of generic drugs; generics comprised 80% of total prescriptions in 2011, up from 63% in 2006.<sup>10</sup> Continued loss of patent protection for prominent drugs—expected to remain significant through 2015—will also continue to lower the growth of spending.<sup>11</sup> While growth has slowed, overall expenditures continue to rise. Moreover, in 2010, 90% of seniors and 57% of non-elderly adults had a prescription drug expense.<sup>12</sup> Additionally, the number of prescribed medicines has increased; from 1999 to 2011, prescriptions rose 43% (from 2.8 billion to 4 billion), outpacing U.S. population growth by 34%.<sup>13</sup> Of note, it was reported in 2012 that the eleven most expensive medicines in the U.S. were for the treatment of rare diseases.<sup>14</sup> With increasing penetrance of prescriptions into all segments of the population, the cost implications for patients, private health insurers, and government payers require attention.

No less significantly, the biomedical industry is an important sector of the U.S. economy, directly employing 1.2 million people with a

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International Trade Administration study, which reported an 18 to 67% increase in the price of best-selling patented drugs in the U.S.).

<sup>7</sup> *CMS 2012 Highlights*, *supra* note 2, at 2.

<sup>8</sup> *Id.*

<sup>9</sup> Kenneth Kaufman, *Bending the Health Care Cost Curve: More than Meets the Eye?* HEALTH AFFAIRS (Apr. 13, 2012), <http://healthaffairs.org/blog/2012/04/13/bending-the-health-care-cost-curve-more-than-meets-the-eye/>.

<sup>10</sup> *Id.*

<sup>11</sup> *Id.*

<sup>12</sup> U.S. Dep't of Health & Human Servs., *Medical Expenditure Panel Survey*, AGENCY FOR HEALTHCARE RES. & QUALITY tbl. 2 (2010), [http://meps.ahrq.gov/mepsweb/data\\_stats/tables\\_compendia\\_hh\\_interactive.jsp?\\_SERVICE=MEPSSocket0&\\_PROGRAM=MEPSPGM.TC.SAS&File=HCFY2010&Table=HCFY2010%5FPLEXP%5FA&VAR1=AGE&VAR2=SEX&VAR3=RACET H5C&VAR4=INSURCOV&VAR5=POVCAT10&VAR6=MSA&VAR7=REGION&VAR8=HEALTH&VARO1=4+17+44+64&VARO2=1&VARO3=1&VARO4=1&VARO5=1&VARO6=1&VARO7=1&VARO8=1&\\_Debug=](http://meps.ahrq.gov/mepsweb/data_stats/tables_compendia_hh_interactive.jsp?_SERVICE=MEPSSocket0&_PROGRAM=MEPSPGM.TC.SAS&File=HCFY2010&Table=HCFY2010%5FPLEXP%5FA&VAR1=AGE&VAR2=SEX&VAR3=RACET H5C&VAR4=INSURCOV&VAR5=POVCAT10&VAR6=MSA&VAR7=REGION&VAR8=HEALTH&VARO1=4+17+44+64&VARO2=1&VARO3=1&VARO4=1&VARO5=1&VARO6=1&VARO7=1&VARO8=1&_Debug=) (last visited Apr. 13, 2014).

<sup>13</sup> *Prescription Drugs: The High Costs of High Costs*, PAYERFUSION.COM CEO'S BLOG (May 14, 2013), <https://payerfusion.com/ceos-blog/prescription-drugs-high-costs/>.

<sup>14</sup> *The 11 Most Expensive Medicines in America*, MEDICAL BILLING & CODING BLOG (Feb. 6, 2012), <http://www.medicalbillingandcoding.org/blog/the-11-most-expensive-medicines-in-america/> (listing Soliris at \$409,500/year; Elaprase at \$375,000/year; Naglazyme at \$365,000/year; Cinryze at \$350,000/year; Folutyn at \$30,000/month; ACTH at \$300,000/year; Myozyme at \$300,000/year; Arcalyst at \$250,000/year; Ceredase/Cerezyme at \$150,000/year; Fabrazyme at \$200,000/year; and Aldurazyme at \$200,000/year).

total output of \$519 billion in 2009.<sup>15</sup> “U.S.-based companies produced nearly 60% of the world’s new medicines, up from 42% the previous decade.”<sup>16</sup> The regulatory apparatus that supports drug development and manufacturing is likewise instrumental in that success. The task of balancing life-science innovation and leadership with meaningful and efficient oversight is as paramount as ever. Yet, new technologies and the recent promise of personalized medicine may necessitate departures from standard models of healthcare regulation. The increasingly patient-centered paradigm, epitomized by the renaissance of the Orphan Drug Act, is potentially an apt laboratory for evaluating efficient, sustainable drug delivery and healthcare systems more broadly.

## II. FOOD AND DRUG ADMINISTRATION (FDA) PRIMER

From snake oil liniment for the masses to Kalydeco for the few, the FDA’s enforcement role in consumer protection has changed considerably over its lifetime. While initially concerned primarily with safety, Congress amended the original Food, Drug and Cosmetic Act (“FDCA”) to include efficacy review in 1962.<sup>17</sup> The FDA’s responsibilities have continued to expand, and “today the agency monitors products that account for twenty-five cents of every dollar in U.S. consumer spending”—including tobacco, food, cosmetics, and drugs.<sup>18</sup>

The FDA is charged with ensuring the safety and efficacy of medical products. Generally, no drug,<sup>19</sup> biologic,<sup>20</sup> or device<sup>21</sup> can be

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<sup>15</sup> Andrew von Eschenbach, *Medical Innovation: How the U.S. Can Retain Its Lead*, WALL ST. J., Feb. 14, 2013, <http://online.wsj.com/article/SB10001424052970203646004577215403399350874.html>; see also ROSS C. DEVOL ET AL., THE GLOBAL BIOMEDICAL INDUSTRY: PRESERVING U.S. LEADERSHIP 1, 16 (Milken Inst. 2011), available at <http://www.ncnano.org/CAMIEExecSum.pdf>.

<sup>16</sup> von Eschenbach, *supra* note 15. The relative contribution of the U.S. to the total scientific output for 88 rare metabolic disorders fell more than 4% from 1996–1998 to 2009–2011, from 28.2% to 23.6% respectively; the second largest contributor, U.K., contributed a 6.6% share. Remco e Vrueth, *China has Joined the Fight Against Rare Disorders* (June 30, 2012), <http://www.rarediseasematters.org/2012/06/china-has-joined-the-fight-against-rare-disorders/>.

<sup>17</sup> Drug Amendments of 1962, Pub. L. No. 87-781, 76 Stat. 780. The Kefauver Harris Amendment passed in the wake of the thalidomide tragedy that occurred in Europe; children were born with birth defects due to their mothers’ use of the drug during pregnancy. *Kefauver-Harris Amendments Revolutionized Drug Development*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm322856.htm> (last updated Apr. 12, 2013).

<sup>18</sup> von Eschenbach, *supra* note 15.

<sup>19</sup> 21 U.S.C. § 321(g) (2012).

The term “drug” means (A) articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to

marketed in the U.S. without FDA approval. Investigational products or test articles typically require submission of an Investigational New Drug application (“IND”) or an Investigational Device Exemption (“IDE”) with the FDA.<sup>22</sup> Subsequent clinical trials are generally divided into three phases.<sup>23</sup> Phase I investigates the safety of the chemical at different dosages in a small cohort of typically healthy volunteers.<sup>24</sup> Phase II expands the study of the test article into a

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affect the structure or any function of the body of man or other animals; and(D) articles intended for use as a component of any article specified in clause (A), (B), or (C).

*Id.*

<sup>20</sup> 42 U.S.C. § 262(i)(1) (2012). Under the Public Health Safety Act (PHS), a biological product is defined as any “virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product . . . applicable to the prevention, treatment, or cure of a disease or condition of human beings.” *Id.* Biologics are treated as drugs for the purpose of Investigational New Drug Applications (IND) requirements. U.S. FOOD & DRUG ADMIN., GUIDANCE FOR CLINICAL INVESTIGATORS, SPONSORS, AND IRBS: INVESTIGATIONAL NEW DRUG APPLICATIONS (INDS)—DETERMINING WHETHER HUMAN RESEARCH STUDIES CAN BE CONDUCTED WITHOUT AN IND 3 (2013), <http://www.fda.gov/downloads/Drugs/Guidances/UCM229175.pdf> [hereinafter GUIDANCE FOR CLINICAL INVESTIGATORS].

<sup>21</sup> 21 U.S.C. § 321(h) (2012).

The term “device” . . . means an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is—

- (1) recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them,
- (2) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
- (3) intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes.

*Id.*

<sup>22</sup> *Investigational New Drug (IND) or Device Exemption (IDE) Process (CBER)*, U.S. FOOD AND DRUG ADMIN., <http://www.fda.gov/biologicsbloodvaccines/developmentapprovalprocess/investigationalnewdrugindordeviceexemptionideprocess/default.htm> (last updated Feb. 2, 2011); see also GUIDANCE FOR CLINICAL INVESTIGATORS, *supra* note 20.

<sup>23</sup> *The FDA’s Drug Review Process: Ensuring Drugs are Safe and Effective*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/drugs/resourcesforyou/consumers/ucm143534.htm> (last updated May 1, 2012). So-called Phase 0 trials constitute exploratory IND studies. See Am. Cancer Soc’y, *Phase 0 Clinical Trials: Exploring if and How a New Drug May Work*, <http://www.cancer.org/treatment/treatmentsandsideeffects/clinicaltrials/whatyouneedtoknowaboutclinicaltrials/clinical-trials-what-you-need-to-know-phase0> (last updated Sept. 21, 2012); see also U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY, INVESTIGATORS, & REVIEWERS: EXPLORATORY IND STUDIES 3 (2006) available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm078933.pdf> (last visited Apr. 13, 2014).

<sup>24</sup> *What are the Phases of Clinical Trials?*, MD ANDERSON CANCER CTR., <http://www.mdanderson.org/patient-and-cancer-information/cancer-information/clinical->

moderately sized patient population, to evaluate safety and potential biological effect.<sup>25</sup> Phase III further expands the number of research participants to investigate the clinical value of the test article.<sup>26</sup> Once Phase III trials have been completed, typically a New Drug Application (“NDA”), Biologic License Application (“BLA”), or a Premarket Approval (“PMA”) application must be submitted by the applicant and filed by the FDA prior to marketing.<sup>27</sup>

Unanticipated complications associated with prominent drugs like Vioxx have pressured the agency to require larger clinical trials and more data from companies to identify even infrequent adverse events.<sup>28</sup> It has been reported that “clinical trials from 2003–2006 were nearly 70% longer than those from 1999–2002.”<sup>29</sup> This environment has seen increasingly complex clinical trials result in increased drug-development costs.<sup>30</sup> Estimates vary considerably, but in 1999, a conservative estimate showed costs on average exceeding \$300 million and more than ten years to bring a drug to market.<sup>31</sup> DiMasi et al. calculated industry expenditure per new drug approved at \$802 million.<sup>32</sup> Including the cost of unsuccessful drug candidates, it has recently been reported that a pharmaceutical company will spend an estimated \$5 billion per new drug successfully brought to

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trials/phases-of-clinical-trials/index.html (last visited Apr. 13, 2014) [hereinafter *Phases of Clinical Trials*].

<sup>25</sup> FDA’s *Drug Review Process*, *supra* note 23; see also *FAQ: What are Clinical Trial Phases?*, U.S. NAT’L LIB. MED., <https://onedrive.live.com/view.aspx?cid=14293ACF9D02CB06&resid=14293ACF9D02CB06!384&app=WordPdf&wdo=1> (last updated Apr. 18, 2008).

<sup>26</sup> See *Phases of Clinical Trials*, *supra* note 24. Post-marketing surveillance or pharmacovigilance is often referred to as Phase IV. Viraj Suvarna, *Phase IV of Drug Development*, 1 PERSPS. IN CLINICAL RES. 57, 57 (2010).

<sup>27</sup> Janice M. Reichert, *Trends in Development and Approval Times for New Therapeutics in the United States*, 2 NATURE REVS. 695, 699 (2003). A former Commissioner of the FDA has recommended that phase III trials essentially be pushed to post-marketing surveillance in order to reduce the cost of bringing a product to market. von Eschenbach, *supra* note 15. This recommendation would essentially return the pre-marketing regulatory process to its original focus surrounding product safety, as opposed to efficacy. Problematically, however, companies likely would still be required to demonstrate effectiveness prior to reaping profits, as insurers increasingly require health technology assessments for inclusion in formularies and providers continue to demand cost-effectiveness research to inform treatment decisions. Also, substantial costs would then be diverted to more robust post-marketing surveillance.

<sup>28</sup> von Eschenbach, *supra* note 15. Despite earlier data indicative of cardiac complications, it was not until 2004 that Merck withdrew Vioxx from the market, after the results of a study to investigate the drug for another purpose—the treatment of colon polyps. Snigdha Prakash & Vikki Valentine, *Timeline: The Rise and Fall of Vioxx*, NATIONAL PUBLIC RADIO (Nov. 10, 2007), <http://www.npr.org/templates/story/story.php?storyId=5470430>.

<sup>29</sup> von Eschenbach, *supra* note 15.

<sup>30</sup> *Id.*

<sup>31</sup> Gary A. Pulsinelli, *The Orphan Drug Act: What’s Right with It*, 15 SANTA CLARA COMPUTER & HIGH TECH. L.J. 299, 304 (1999).

<sup>32</sup> Joseph A. DiMasi et al., *The Price of Innovation: New Estimates of Drug Development Costs*, 22 J. HEALTH ECON. 151, 180 (2003) (in 2000 dollars).

market.<sup>33</sup> These costs, necessarily passed on to patients and payors, impact the overall expense of healthcare in the U.S. Additionally, for better or worse, notably absent from the FDA's regulatory mandate is any consideration of therapy cost or cost-effectiveness. Moreover, subsequent formulary decisions and treatment recommendations made by payors and providers, respectively, are completely removed from the FDA approval process.<sup>34</sup>

The impact of a protracted and complex regulatory process also potentially threatens innovation and the economy more pervasively. A 2012 survey found approximately 80% of life sciences CEOs did not believe that "the FDA regulatory approval process 'is the best in the world,' and 81% believed that 'within five years, another country could conceivably recreate the ecosystem that has made the U.S. the leading biomedical region in the world.'"<sup>35</sup> Obviously, such a drastic scenario could threaten the loss of jobs and domestic capacity for research and development.<sup>36</sup>

### III. THE FDA AND INTELLECTUAL PROPERTY RIGHTS

There are many available means to protect intellectual property in the pharmaceutical and biotechnology industries. Most prominently, patents generally provide owners the right to exclude others from various activities, including sale of the protected product, for a term of 20 years.<sup>37</sup> Since a patent is filed prior to initiation of the FDA regulatory process, much of the fixed patent term will be lost because the patent owner cannot exploit its monopoly power without FDA approval to market the product. Appreciating the increasingly protracted approval process, Congress passed the Drug Price

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<sup>33</sup> Matthew Herper, *The Cost Of Creating A New Drug Now \$5 Billion, Pushing Big Pharma To Change*, FORBES (Aug. 11, 2013), <http://www.forbes.com/sites/matthewherper/2013/08/11/how-the-staggering-cost-of-inventing-new-drugs-is-shaping-the-future-of-medicine/>; see also Matthew Herper, *The Truly Staggering Cost Of Inventing New Drugs*, FORBES (Feb. 10, 2012), <http://www.forbes.com/sites/matthewherper/2012/02/10/the-truly-staggering-cost-of-inventing-new-drugs/>.

<sup>34</sup> This has the potential to create circumstances in which FDA-approved drugs are nonetheless unavailable to patients due to subsequent health technology assessments. For example, physicians at Sloan Kettering Memorial Hospital have refused to prescribe the drug, Zaltrap, which is more expensive and has not been shown to be more cost effective than alternatives. Peter B. Bach et al., *In Cancer Care, Cost Matters*, N.Y. TIMES, Oct. 14, 2012, at A25, <http://www.nytimes.com/2012/10/15/opinion/a-hospital-says-no-to-an-11000-a-month-cancer-drug.html>.

<sup>35</sup> von Eschenbach, *supra* note 15 (quoting CAL. HEALTHCARE INST., 2012 CALIFORNIA BIOMEDICAL INDUSTRY REPORT 26 (2012)).

<sup>36</sup> *Id.*

<sup>37</sup> See generally, U.S. PAT. & TRADEMARK OFF., *General Information Concerning Patents*, [http://www.uspto.gov/patents/resources/general\\_info\\_concerning\\_patents.jsp](http://www.uspto.gov/patents/resources/general_info_concerning_patents.jsp) (last visited Apr. 13, 2014).



Competition and Patent Term Restoration Act of 1984 (commonly known as Hatch-Waxman).<sup>38</sup> The statute enables the owners of patents on certain human drugs, biologics, and medical devices to restore to the terms of those patents some of the time lost while awaiting . . . government approval.<sup>39</sup> The rights derived from extension of the patent term are limited to the product approved. Subject to various deductions and limitations, the patent term is generally extended by the time equal to the duration of the testing and regulatory period after the patent issued, but, when added to the remaining life of the patent, not to exceed fourteen years.<sup>40</sup> Of note, the pharmaceutical industry has not brought to market new blockbuster therapies as quickly as its patents are expiring.<sup>41</sup>

Distinct from market monopoly based on patent, Congress has enabled the FDA to grant exclusivity periods to incentivize various types of drug testing. Under such a regimen, the FDA generally will not grant market approval to follow-on products for a specified term, eliminating competition and creating monopoly pricing power during that time.<sup>42</sup> For example, the Hatch-Waxman Act created a 180-day exclusivity period for the first generic manufacturer to file an abbreviated NDA (“ANDA”) challenging an innovator’s drug patent.<sup>43</sup>

There are distinct differences between these two forms of protection. Patents provide broader protection, since the scope is not necessarily limited to a specific use.<sup>44</sup> While both spur investment and

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<sup>38</sup> Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman), Pub. L. No. 98-417, 98 Stat. 1585 (codified at scattered sections of 15, 21, 28, and 35 U.S.C.).

<sup>39</sup> 35 U.S.C. § 156 (2012); U.S. PAT. & TRADEMARK OFF., U.S. DEP’T OF COMMERCE, MANUAL OF PATENT EXAMINING PROCEDURE § 2750 (9th ed. Mar. 2014). On December 3, 1993, 35 U.S.C. § 156 was further amended to provide for interim extension of a patent’s term where a product embodied in the claim(s) was expected to receive FDA approval, but not until after the original expiration date. *Id.*

<sup>40</sup> 35 U.S.C. § 156(c) (2012). The USPTO calculates the extension term based on the testing and approval phases of the FDA’s regulatory review process. *Id.* The testing phase is calculated from the time the IND application is filed, and the approval phase is calculated from the time the NDA is submitted to the FDA. *Id.* The formula allows the patent holder to recuperate half of the testing phase and the entire approval phase toward a maximum of a five-year patent extension but no more than fourteen years from the date of NDA approval. *Id.*

<sup>41</sup> C.H., *Health spending Cost Curve, Slightly Bent*, ECONOMIST (Jan. 11, 2012), <http://www.economist.com/blogs/democracyinamerica/2012/01/health-spending>; see also George J. Brewer, *Drug Development for Orphan Diseases in the Context of Personalized Medicine*, 154 TRANSLATIONAL RES. 314, 320 (2009).

<sup>42</sup> Wendy H. Schacht & John R. Thomas, *Follow-On Biologics: The Law and Intellectual Property Issues*, CONGRESSIONAL RES. SERV. (Dec. 6, 2012), <http://www.fas.org/sgp/crs/misc/R41483.pdf>

<sup>43</sup> 21 C.F.R. § 314.107(c)(1) (2009); see also U.S. FOOD & DRUG ADMIN. CENTER FOR DRUG EVALUATION AND RES. (CDER), GUIDANCE FOR INDUSTRY, 180-DAY GENERIC DRUG EXCLUSIVITY UNDER THE HATCH-WAXMAN AMENDMENTS TO THE FEDERAL FOOD, DRUG, AND COSMETIC ACT 1 (June 1998), available at <http://www.fda.gov/downloads/Drugs/.../Guidances/ucm079342.pdf>.

<sup>44</sup> See Enrique Seoane-Vazquez et al., *Incentives for Orphan Drug Research and Development in the United States*, 3 ORPHANET J. RARE DISEASES 33 (2008).

venture capital, market exclusivity has a few advantages over patents.<sup>45</sup> First, the former does not necessarily reward innovation like a patent. There are typically no requirements that the product for which exclusivity is granted be novel or non-obvious—though no doubt having utility based on demonstrated effectiveness when used as indicated in the associated labeling.<sup>46</sup> Unlike the five years of data exclusivity provided for by the Hatch-Waxman Act, the exclusivity afforded by the Orphan Drug Act is independent of product classification as a new chemical entity.<sup>47</sup> Second, the duration of marketing exclusivity does not run during development and FDA review, as the life of a patent begins to run from the filing date.<sup>48</sup> Third, market exclusivity is less susceptible to litigation, and the FDA, in essence, is responsible for policing the market by limiting approvals. As a result, both the market exclusivity and the patent can be leveraged to create monopoly power in the market, and orphan products are no exception.

#### IV. RARE DISEASE AND THE ORPHAN DRUG ACT (“ODA”)<sup>49</sup>

The public health implications of rare disease are significant. The National Institutes of Health has identified nearly 7,000 such rare diseases, and it is estimated that 250 new rare diseases are described annually.<sup>50</sup> Together these conditions affect approximately 25–30

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<sup>45</sup> Christopher A. Cotropia, *The Folly of Early Filing in Patent Law*, 61 HASTINGS L.J. 65, 84 (2009). Of note, it will be interesting to see if market exclusivity has more importance in light of potential repercussions arising from the recent *Myriad* decision. See generally, *Assoc. for Molecular Pathology, et al. v. Myriad Genetics, Inc., et al.*, 569 U.S. \_\_\_ (2013).

<sup>46</sup> Marlene E. Haffner et al., *Two Decades of Orphan Product Development*, 1 NATURE REV. 821, 821 (2002).

<sup>47</sup> Kate Greenwood, Turning “Recycled Molecules” into Orphan Drugs: Time to Experiment with Calibrated Incentives? 3 (final conference draft) (available upon request).

<sup>48</sup> *Id.*; Cotropia, *supra* note 45, at 81.

<sup>49</sup> Orphan Drug Act, Pub. L. No. 97-414, § 1(b)(4), 96 Stat. 2049 (1983) (codified principally at 21 U.S.C. § 360aa–360ee). Apparently, “Quincy, M.E.” publicized the problem relating to the paucity of treatments for rare diseases and garnered much support for the plight just prior to the passage of the ODA. Alexander Gaffney, *30 Years Later, FDA Looks Back on Passage of the Orphan Drug Act*, REGULATORY FOCUS (Jan. 4, 2013), <http://www.raps.org/focus-online/news/news-article-view/article/2686/30-years-later-fda-looks-back-on-passage-of-orphan-drug-act.aspx>. The issue continues to find traction in popular culture, notably with the film “Extraordinary Measures” (2010) and, very recently, in the television show “The Blacklist.” An episode of the latter portrayed a bioterrorist bent on infecting larger segments of the population with a rare disease afflicting his son, in order to create incentive for the pharmaceutical industry to develop a cure. See Jason Evans, *The Blacklist’ Recap, Season 1, Episode 7, ‘Frederick Barnes’*, WALL ST. J., Nov. 4, 2013, <http://blogs.wsj.com/speakeasy/2013/11/04/the-blacklist-recap-season-1-episode-7-frederick-barnes/>.

<sup>50</sup> *Frequently Asked Questions*, U.S. DEP’T OF HEALTH & HUMAN SERVS., OFFICE OF RARE DISEASES RESEARCH, <http://rarediseases.info.nih.gov/about-ordr/pages/31/frequently-asked-questions> (last visited Apr. 13, 2014); Olivier Wellman-Labadie & Youwen Zhou, *The US Orphan*

million people in the U.S. and an estimated 350 million worldwide.<sup>51</sup> Approximately 80% of all rare diseases are genetic.<sup>52</sup> Fifty percent of those affected in the U.S. are children, and 35% of deaths in the first year of life are attributable to rare disease.<sup>53</sup> Less than five percent of rare diseases currently have a treatment; 95% of rare diseases lack a single FDA-approved therapy.<sup>54</sup> Therefore, orphan drugs are an important issue for approximately one in ten people in the U.S.—not including family members, caregivers, and advocacy groups.

The expense of drug development coupled with limited return on investment created little incentive for the pharmaceutical industry to develop products that affected only small populations. This economic reality results in “drug loss,” or the opportunity cost measured in additional therapies that might otherwise have been brought to market but for prolonged regulatory processes and pursuit of candidate drugs with only highly profitable margins.<sup>55</sup> As a result, Abbey Myers helped form a coalition which successfully advocated for legislation and which later became the National Organization for Rare Diseases (“NORD”).<sup>56</sup> Congress acted to incentivize research surrounding these so-called orphaned conditions, to encourage companies to parent such test articles through the regulatory process. The moniker “orphan,” expresses the neglect that derives from the unwillingness of sponsors to develop and bring to market treatments for rare disease due to lack of profitability.<sup>57</sup> The Orphan Drug Act passed in 1982, and was signed into law by President Reagan in January 1983.<sup>58</sup>

Pursuant to the Act, drugs and biologics may be conferred orphan status if intended for the safe and effective treatment, diagnosis, or prevention of rare diseases/disorders that affect (1) fewer than 200,000 people in the United States or (2) more than 200,000 people, but for which there is nonetheless “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

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*Drug Act: Rare Disease Research Stimulator or Commercial Opportunity?*, 95 HEALTH POLICY 216, 217 (2010).

<sup>51</sup> Kiran N. Meekings et al., *Orphan Drug Development: an economically viable strategy for biopharma R&D*, 17 DRUG DISCOVERY TODAY 660 (2012).

<sup>52</sup> PhRMA, RARE DISEASES: A REPORT ON ORPHAN DRUGS IN THE PIPELINE, MEDS. IN DEV. 2013 REPORT 7 (2013), available at [http://phrma.org/sites/default/files/pdf/Rare\\_Diseases\\_2013.pdf](http://phrma.org/sites/default/files/pdf/Rare_Diseases_2013.pdf).

<sup>53</sup> *Id.* at 4.

<sup>54</sup> *Id.* at 7.

<sup>55</sup> Michael Tennent, *The FDA, Neither Safe nor Effective*, NEW AM. (Sept. 16, 2010, 1:00 A.M.), <http://www.thenewamerican.com/usnews/health-care/item/1805-the-fda-neither-safe-nor-effective>; see also *Glossary*, FDA REVIEW.ORG, [http://www.fdareview.org/glossary.shtml#drug\\_lag](http://www.fdareview.org/glossary.shtml#drug_lag) (last visited Apr. 13, 2014).

<sup>56</sup> See generally *Vision and Mission*, NORD, <https://www.rarediseases.org/about/vision-mission> (last visited December 13, 2013).

<sup>57</sup> 21 C.F.R. § 316.3(b)(10) (2013). The term is specifically defined in the regulations to mean “a drug intended for use in a rare disease or condition as defined in section 526 of the act.” *Id.*

<sup>58</sup> Haffner et al., *supra* note 46, at 821.

such drug.”<sup>59</sup> Various amendments to the legislation have been passed since enactment. The original version of the ODA defined a rare disease or condition using only the second prong of the current definition.<sup>60</sup> However, drug sponsors were reluctant to invest the time and money required to demonstrate commercial infeasibility and were loath to disclose cost and expected revenue data to the FDA.<sup>61</sup> As a result of this uncertainty, the first prong was added by 1984 amendment.<sup>62</sup> This rarity determination is typically based on the prevalence of the disease.<sup>63</sup> The sponsor bears the burden of providing a rationale to meet the requisite rarity.<sup>64</sup> Importantly, in addition to a disease with prevalence less than 200,000, a sponsor may also seek orphan designation for a drug that targets a particular subset of a disease that otherwise would not satisfy the statutory limit.<sup>65</sup> Also, since only drugs that were not protected or eligible for a patent could be granted exclusivity under the ODAs originally enacted—as patents were viewed as a sufficient catalyst—Congress again amended the Act in 1985 to extend its application to drugs that are patent-protected.<sup>66</sup> Orphan drug designation can only be granted if received prior to the application for marketing approval.<sup>67</sup>

Congress has devised many incentives for developing orphan products. Legislation provides marketing exclusivity, NDA fee waivers,<sup>68</sup> tax credits for related research, grant funding for study of treatments for rare diseases, and eligibility for various types of

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<sup>59</sup> 21 C.F.R. §§ 316.21(a)(1), (c) (2012); 21 C.F.R. § 316.10(b)(8)(ii) (1993); 21 U.S.C. § 360bb(b)(2) (2012).

<sup>60</sup> Pulsinelli, *supra* note 31, at 306.

<sup>61</sup> *Id.* at 307.

<sup>62</sup> *Id.* Similarly, the humanitarian use device (“HUD”) program applies to a device that is intended to treat or diagnose a disease or condition that affects fewer than 4,000 individuals in the U.S. per year. See 21 C.F.R. § 814.3(n) (2013). A successful applicant would then receive a humanitarian device exemption (HDE). *Id.* § 814.3(m).

<sup>63</sup> 21 C.F.R. § 316.21(b) (2012). Prevalence is defined in the Act as the number of persons in the U.S. who have been diagnosed as having the condition at the time of submission of the request for orphan designation. *Id.* Incidence may be used to calculate the number of individuals affected by acute conditions. *Frequently Asked Questions*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/HowtoapplyforOrphanProductDesignation/ucm240819.htm> (last updated January 22, 2013).

<sup>64</sup> Haffner, *supra* note 46, at 824. See also 21 C.F.R. §§ 316.20, 316.21 (detailing submission requirements for orphan-drug designation).

<sup>65</sup> Haffner, *supra* note 46, at 824. Interestingly, the 200,000 threshold was selected in relationship to the estimated prevalence of narcolepsy and multiple sclerosis. DEP’T OF HEALTH & HUMAN SERVS., OFF. OF INSPECTOR GEN., THE ORPHAN DRUG ACT: IMPLEMENTATION AND IMPACT 4 (2001), available at <http://oig.hhs.gov/oei/reports/oei-09-00-00380.pdf> [hereinafter OIG, ODA].

<sup>66</sup> Orphan Drug Amendments of 1985, Pub. L. No. 99-91, 99 Stat. 387 (1985).

<sup>67</sup> Orphan Drug Regulations, 78 Fed. Reg. 35,118, 35,133 (June 12, 2013) (to be codified at 21 C.F.R. pt. 316) [hereinafter Orphan Drug Regulations].

<sup>68</sup> OIG, ODA, *supra* note 65, at 8. NDA fee waivers are a component of the Prescription Drug User Fee Act (PDUFA). In 2001, this amounted to approximately \$500,000. *Id.* at 4.

expedited review.<sup>69</sup> Also, open trials allow for wider access while studies are ongoing.<sup>70</sup> By 2008, over half of drugs in the fast track program<sup>71</sup> had orphan designations, and approximately one quarter of the fifty fastest drug approvals have been for orphan products.<sup>72</sup> Yet, Seoane-Vazquez et al. found that the difference in FDA-review time between orphan and non-orphan NMEs was not statistically significant when divided into priority and standard review.<sup>73</sup> Thus, while more amenable to expedited review, it is not clear that orphan products are reviewed any more quickly than non-orphan products under expedited review.

Marketing exclusivity is widely regarded as the most powerful incentive.<sup>74</sup> Exclusivity assures that the FDA will not approve the same drug for the same indication over a seven year period after marketing approval of the original product.<sup>75</sup> A manufacturer of an orphan drug is only protected from competition from other manufacturers seeking to sell the same drug for the treatment of the same orphan disease.<sup>76</sup> The ODA's grant of exclusivity has three exceptions.<sup>77</sup> First, a subsequent applicant's request for orphan designation can be granted if that sponsor demonstrates a plausible hypothesis that the drug, while otherwise the same chemical as a previously designated orphan drug, is yet clinically superior.<sup>78</sup> Second,

<sup>69</sup> Haffner, *supra* note 46, at 821.

<sup>70</sup> Pulsinelli, *supra* note 31, at 312; *see also* 21 U.S.C. § 360dd (1983).

<sup>71</sup> *See Fast Track, Breakthrough Therapy, Accelerated Approval and Priority Review*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/forconsumers/byaudience/forpatientadvocates/speedingaccessstoimportantnewtherapies/ucm128291.htm> (last updated June 26, 2013). Section 112, "Expediting study and approval of fast track drugs," of the Food and Drug Administration Modernization Act of 1997 ("FDAMA") mandates the Agency to facilitate the development and expedite review of drugs and biologics intended to treat serious or life-threatening conditions and that demonstrate the potential to address unmet medical needs. *Id.*; *see also* U.S. FOOD & DRUG ADMIN., EXPEDITED PROGRAMS FOR SERIOUS CONDITIONS—DRUGS AND BIOLOGICS 9 (Jun. 2013), <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>.

<sup>72</sup> Kurt Samson, *Orphan Economics: The Downside of Supply-side Pharmacology*, ANNALS NEUROLOGY, Sept. 2008, at A16.

<sup>73</sup> Seoane-Vazquez et al., *supra* note 44 ("Statistically significant . . . differences in favor of orphan NMEs were found for the use of any Fast Track or Subparts E/H review procedures (29.5% vs. 9.5%), and also for NMEs given priority review by the FDA (83.5% vs. 35.4%).").

<sup>74</sup> Haffner, *supra* note 46, at 821; *see also* OIG, ODA, *supra* note 65 at 8–9.

<sup>75</sup> OIG, ODA, *supra* note 65, at 8–9; *see also* Sigma-Tau Pharms. v. Schwetz, 288 F.3d 141, 145 (4th Cir. 2002) ("By using the words 'such drug for such disease or condition,' Congress made clear its intention that § 360cc(a) was to be disease-specific, not drug-specific. In other words, the statute as written protects uses, not drugs for any and all uses.").

<sup>76</sup> 21 C.F.R. § 316.34 (2013).

<sup>77</sup> Pulsinelli, *supra* note 31, at 311.

<sup>78</sup> 21 C.F.R. § 316.20(a) (2013). There are different definitions for determining the sameness of molecules, depending on their size. 21 C.F.R. § 316.3(b)(14) (2013).

the FDA can approve additional applications for the same drug “if . . . the holder of the approved application . . . or of the license cannot assure the availability of sufficient quantities of the drug to meet the needs of persons with the disease or condition for which the drug was designated.”<sup>79</sup> Third, the statute allows the FDA to approve additional applications based on consent of the original designee.<sup>80</sup>

It is worth pausing to note that even after the exclusivity period expires, there is less incentive for other competitors to join the market, due to the limited market size.<sup>81</sup> In contrast, once a pharmaceutical company identifies a profitable segment of the wider market, competitors are apt to enter that market in an attempt to capture a significant market share—a larger market can obviously accommodate more competitors because the return is still divisible into substantial portions. Marlene Haffner, a former director of the FDA’s Office of Orphan Products Development (“OOPD”), has observed: “[w]ith the chronicity of rare diseases and a drug that, for the most part, won’t have competition—it’s yours and it’s yours beyond the seven-year exclusivity[.] Money can be made.”<sup>82</sup>

The Biotechnology Industry Organization (“BIO”) released a 2012 statement emphasizing the importance of the other incentive measures as well.<sup>83</sup> Sponsors receive a tax credit for 50% of the cost of

*Clinically superior* means that a drug is shown to provide a significant therapeutic advantage over and above that provided by an approved drug (that is otherwise the same drug) in one or more of the following ways:

- (i) Greater effectiveness than an approved drug (as assessed by effect on a clinically meaningful endpoint in adequate and well controlled clinical trials). Generally, this would represent the same kind of evidence needed to support a comparative effectiveness claim for two different drugs; in most cases, direct comparative clinical trials would be necessary; or
- (ii) Greater safety in a substantial portion of the target populations, for example, by the elimination of an ingredient or contaminant that is associated with relatively frequent adverse effects. In some cases, direct comparative clinical trials will be necessary; or
- (iii) In unusual cases, where neither greater safety nor greater effectiveness has been shown, a demonstration that the drug otherwise makes a major contribution to patient care.

21 C.F.R. § 316.3(b)(3) (2013).

<sup>79</sup> 21 U.S.C. § 360cc(b)(1) (2013); *see also* 21 C.F.R. § 316.36(a) (2014).

<sup>80</sup> 21 C.F.R. § 316.36(b) (2014).

<sup>81</sup> OIG, ODA, *supra* note 65, at 9 (“The market for most orphan products is not highly competitive . . .”); *see also* Seoane-Vazquez et al., *supra* note 44 (“Orphan NMEs had significantly less . . . generic competition than other NMEs.”).

<sup>82</sup> Samson, *supra* note 72, at A16.

<sup>83</sup> *Orphan Drugs: BIO Submits Comments on Orphan Drug Regulations*, BIOTECHNOLOGY INDUS. ORG. (Jan. 17, 2012), <http://www.bio.org/advocacy/letters/orphan-drugs-bio-submits-comments-orphan-drug-regulations> [hereinafter *Orphan Drugs*, BIO]. According to the organization’s website,

conducting clinical trials of orphan drugs.<sup>84</sup> The Office of Management and Budget (“OMB”) has estimated that the value of the tax credit could rise from approximately \$470 million in 2010 to over \$1 billion in 2016.<sup>85</sup>

The ODA is administered through the OOPD, which sponsors have regarded as a valuable resource.<sup>86</sup> The OOPD provides study-design assistance.<sup>87</sup> Office funding is appropriated and distributed specifically for the clinical research of drugs, biological products, foods, and devices that are used to treat rare diseases. The OOPD attempts to respond to requests for orphan designation within sixty days, but the office has no role in the drug approval process.<sup>88</sup> In the first year of orphan grant funding, Congress appropriated \$500,000, from which eight studies were funded.<sup>89</sup> As of 2002, twenty-one grants were awarded to investigators at academic institutions, while startup firms received the remaining grants; the OOPD program was the largest single source of extramural clinical grants at the FDA.<sup>90</sup> By 2010, the funding amount increased to \$14.1 million.<sup>91</sup> Recently, the FDA has apportioned the funding between ten to fifteen grantees.<sup>92</sup> Through 2012, forty-five products supported by the OOPD grants program have

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This includes recognizing that while market exclusivity of approved orphan products is a major incentive to the development of drugs for rare diseases, the other statutory incentives that arise from designation—such as tax credits, research grants, and exemptions from the usual drug application user fees—are equally important in securing and sustaining the necessary capital investments to develop orphan drugs.

*Id.* Ten others also submitted comments to a proposed FDA rule, including PhRMA, Pfizer, GlaxoSmithKline, and Novartis. See *Orphan Drug Regulations*, REGULATIONS.GOV, <http://www.regulations.gov/#!docketBrowser;rpp=25;po=0;dc=PS;D=FDA-2011-N-0583> (last visited December 12, 2013).

<sup>84</sup> Greenwood, *supra* note 47, at 4. The tax credit is useful to start-up companies without taxable income, due to a twenty-year “carry forward” and a one-year “fall-back” provision. *Id.* Providing flexibility, a sponsor may apply the credit to the taxes owed in a year during which related costs are incurred. *Id.*

<sup>85</sup> Greenwood, *supra* note 47, at 4.

<sup>86</sup> OIG, ODA *supra* note 65, at 2. The NIH also has an Office of Rare Disease Research (ORDR). See *About ORDR*, OFF. OF RARE DISEASES RES., <http://rarediseases.info.nih.gov/>; see also Harald E. Heemstra et al., *Characteristics of Orphan Drug Applications that Fail to Achieve Marketing Approval in the USA*, 16 DRUG DISCOVERY TODAY 73 (2011).

<sup>87</sup> Seoane-Vazquez et al., *supra* note 44.

<sup>88</sup> OIG, ODA, *supra* note 65, at 5. In 2000, the average time to designate an orphan product was 160 days. *Id.* at 11.

<sup>89</sup> Haffner, *supra* note 46, at 822.

<sup>90</sup> *Id.*

<sup>91</sup> *FAQ Concerning the Orphan Products Grants Program*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/WhomtoContactaboutOrphanProductDevelopment/ucm224956.htm> (last updated Nov. 2, 2010).

<sup>92</sup> Greenwood, *supra* note 47, at 4.

been approved for marketing.<sup>93</sup> While of uncertain impact for orphan drug approval specifically, the FDA expected to lose \$209 million in the 2013 fiscal year—\$126 million in budget authority and \$83 million in user fees—due to sequestration.<sup>94</sup>

These measures arguably have proven successful in creating investment in the orphan space.<sup>95</sup> In the ten years that preceded enactment of the ODA, only ten products were approved for the treatment of rare disease.<sup>96</sup> By 2002, more than 1,000 drug and biologic products had received orphan drug designation; the FDA had approved 231 products (fifty biologics) for marketing.<sup>97</sup> By 2013, thirty years after the ODA's passage, the FDA has designated 2,979 products as "orphan drugs" and approved 456 for marketing.<sup>98</sup> Ronald Reagan hailed the legislation as "one of the most significant and successful pieces of healthcare legislation during [his] presidency."<sup>99</sup>

It is apparent that an increasing number of companies are availing themselves of the ODA with success. Wellman-Labadie and Zhou found that 73% of orphan-designated products are sponsored by an array of biotechnology firms, indicating the importance of the ODA in stimulating smaller businesses in the life sciences.<sup>100</sup> In 2011, it was estimated that the orphan drug market was worth more than \$50 billion, and the market "turns out blockbusters at the same rate as the

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<sup>93</sup> *Developing Products for Rare Diseases & Conditions*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/default.htm> (last updated June 25, 2012).

<sup>94</sup> Margaret A. Hamburg, *2013 FDLI Annual Conference*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/NewsEvents/Speeches/ucm349118.htm> (last updated Apr. 23, 2013); see also Elizabeth M. Wroe & Philip S. Bonforte, *September Sequester Surprise: FDA User Fees on the Chopping Block*, 10 PHARM. LAW & INDUS. REPORT 1332, 1332 (2012), available at [http://www.faegrebdc.com/webfiles/FDA\\_Bloomberg.pdf](http://www.faegrebdc.com/webfiles/FDA_Bloomberg.pdf).

<sup>95</sup> But see Seoane-Vazquez et al., *supra* note 44 (enumerating alternative explanations for recent increase in orphan products); Marlene E. Haffner et al., *Does Orphan Drug Legislation Really Answer the Needs of Patients?*, 371 LANCET 2041, 2041 (2008).

<sup>96</sup> Haffner, *supra* note 46 at 824.

<sup>97</sup> *Id.* at 821.

<sup>98</sup> *Search Orphan Drug Designations and Approvals*, U.S. FOOD & DRUG ADMIN., <http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm> (last visited December 13, 2013). This number has now increased to 457 approved products in total of 3052 designated products. *Id.*

<sup>99</sup> Paul D. Maher & Marlene Haffner, *Orphan Drug Designation and Pharmacogenomics*, 20 BIODRUGS 71, 72 (2006).

<sup>100</sup> Wellman-Labadie & Zhou, *supra* note 50 (finding that the top ten biotechnology firms of 2008 only accounted for 12% of all biotech-sponsored products with orphan designations and, though biotech firms account for roughly half of orphan-product approvals, the top ten firms only sponsor 15% of those products).



broader industry.”<sup>101</sup> Forty-three products with orphan designation have exceeded \$1 billion in annual revenue.<sup>102</sup>

In a 2012 study, Meekings found that the 2001–2010 compound annual growth rate (“CAGR”) in orphan drug designations was approximately 10%, compared with a negative CAGR for new molecular entities (“NMEs”) overall for the same period.<sup>103</sup> Meekings reported that orphan drugs represented approximately 30% of NME approvals in 2010.<sup>104</sup> According to the study, orphan drugs have the same revenue-generating potential as non-orphan drugs.<sup>105</sup> This analysis suggests that the impact of a smaller patient population is offset by the higher pricing, the increased market share, the longer exclusivity period, and the faster uptake rate that orphan drugs often garner as a result of the high unmet medical need for many of these diseases.<sup>106</sup> Of the 192 drugs selected for the study, 15% had multiple designations, and there was greater than a four-fold increase in profit associated with having more than one orphan designation.<sup>107</sup> While some drugs that are first approved for non-orphan diseases subsequently received designation for treatment of orphan disease, roughly 75% of the studied drugs targeted an orphan disease indication first.<sup>108</sup> Slightly more than 8% of orphan drugs subsequently received approval for treatment of larger non-orphan diseases.<sup>109</sup> Finally, using international data, the study also suggested that clinical trials for orphan products are shorter and more successful.<sup>110</sup>

Still, others have also posited that the costs associated with research and development and marketing of orphan drugs are significantly less than for standard drugs.<sup>111</sup> Since most orphan drugs are designated to treat serious or life threatening conditions, expedited

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<sup>101</sup> Katie Thomas, *Making ‘Every Patient Counts’ a Business Imperative*, N.Y. TIMES, Jan. 30, 2013, [http://www.nytimes.com/2013/01/31/business/orphan-drugs-for-rare-diseases-gain-popularity-with-pharmaceutical-companies.html?\\_r=0](http://www.nytimes.com/2013/01/31/business/orphan-drugs-for-rare-diseases-gain-popularity-with-pharmaceutical-companies.html?_r=0) (citing *The Economic Power of Orphan Drugs*, THOMSON REUTERS (2012), [http://thomsonreuters.com/products/ip-science/04\\_013/1001450.pdf](http://thomsonreuters.com/products/ip-science/04_013/1001450.pdf)).

<sup>102</sup> Wellman-Labadie & Zhou, *supra* note 50 (noting that 18 products received approval solely for an orphan indication and eleven of those reached \$1 billion in sales within the exclusivity period, including Gleevec). Additionally, for products with non-orphan indications, seven received orphan designation during or following the year in which sales generated \$1 billion. *Id.* tbl. 3.

<sup>103</sup> Meekings et al., *supra* note 51, at 660.

<sup>104</sup> *Id.*; but see Seoane-Vazquez et al., *supra* note 44 (finding that 115 of 635 NMEs (18.1%) approved from 1983 to 2007 were for orphan indications).

<sup>105</sup> Meekings et al., *supra* note 51, at 661.

<sup>106</sup> *Id.*

<sup>107</sup> *Id.* at 662.

<sup>108</sup> *Id.*

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

<sup>110</sup> *Id.* at 663. The results showed more than a one-year difference development time from phase II to market and a 5% greater probability of success. *Id.*

<sup>111</sup> André Côté & Bernard Keating, *What Is Wrong with Orphan Drug Policies?*, 15 VALUE IN HEALTH 1185, 1189 (2012).

review is available, as noted previously.<sup>112</sup> Illustratively, in January 2001, imatinib (Gleevec®) received orphan drug designation for treatment of chronic myelogenous leukemia.<sup>113</sup> In a Phase I study, remission was achieved in each of the first 31 patients treated.<sup>114</sup> Under accelerated review, imatinib received FDA approval, with Phase II trials still ongoing, in less than three months and was first marketed in May 2001.<sup>115</sup>

Also, fewer research participants are enrolled in the studies; smaller clinical trials have both positive and negative consequences. In the late 1980s, severe combined immunodeficiency (“SCID”) was estimated to affect approximately twelve patients in the U.S.; six affected children were enrolled in a clinical trial of pegademase (Adagen).<sup>116</sup> Pegademase showed efficacy in each participant and was subsequently approved by the FDA in 1990.<sup>117</sup> The FDA can review less data more quickly.<sup>118</sup> Of competing concern, smaller data sets result in less reliable conclusions regarding safety and efficacy.<sup>119</sup>

These efficiencies are offset to some degree by other factors as well.<sup>120</sup> Finding eligible research participants is an ongoing problem for investigators involved in orphan-product development.<sup>121</sup> The relative scarcity often necessitates conducting trials in multiple locations. The disadvantages of using multiple sites include maintaining consistency across centers, increased cost (e.g. travel), and increased administrative time required for coordination across multiple centers.<sup>122</sup> In some cases, considerable burden is placed on patients who travel a substantial distance to obtain treatment if it is only available at a single site.<sup>123</sup>

Some trends emerged over the first twenty years of the ODA, “with [approximately] 85% of orphan designations being used for the treatment of serious and/or life-threatening diseases.”<sup>124</sup> Oncology products have received the highest percentage of orphan designations, while metabolic disorders represent the second largest group.<sup>125</sup> Approximately half of all orphan products were approved for pediatric

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<sup>112</sup> Haffner et al., *supra* note 46, at 823.

<sup>113</sup> Maher & Haffner, *supra* note 99, at 76.

<sup>114</sup> *Id.*

<sup>115</sup> *Id.*

<sup>116</sup> *Id.* at 75.

<sup>117</sup> *Id.*

<sup>118</sup> Haffner et al., *supra* note 46, at 823.

<sup>119</sup> *Id.*

<sup>120</sup> See generally, Erik Tambuyzer, *Rare Diseases, Orphan Drugs and Their Regulation: Questions and Misconceptions*, 9 NATURE REVS. 921, 921–22 (2010).

<sup>121</sup> Haffner et al., *supra* note 46, at 823.

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

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

<sup>124</sup> *Id.* at 822.

<sup>125</sup> *Id.* (31% for rare form of cancer, and 11% for metabolic disorders).

use.<sup>126</sup> Additionally, “nearly half of all the biological products that ha[d] been approved for marketing in the [U.S. were] designated orphan products.”<sup>127</sup> As of 2002, approximately only 20% of orphan designations were for novel biotechnology products.<sup>128</sup> Genentech,<sup>129</sup> Amgen,<sup>130</sup> and Genzyme<sup>131</sup> share the distinction of each having orphan drugs as their first products to receive marketing approval.<sup>132</sup> Companies such as BioMarin Pharmaceutical<sup>133</sup> specialize solely in orphan-product research and development.<sup>134</sup>

In 2001, the Office of Inspector General (“OIG”) of Health and Human Services (“HHS”) issued a report, concluding that the implementation of the ODA had not raised significant access concerns, though recognizing that the drugs can be expensive and in limited supply.<sup>135</sup> No regulatory or legislative changes were recommended at that time.<sup>136</sup> The ODA has been widely regarded as successfully bringing therapies to market to treat rare diseases.<sup>137</sup> At least one

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<sup>126</sup> *Id.*

<sup>127</sup> *Id.*

<sup>128</sup> *Id.*; but see Wellman-Labadie & Zhou, *supra* note 50, at 219, 221–22 (finding that of the 616 unique pharmaceutically active agents with orphan designation through 2009, 82% were NMEs).

<sup>129</sup> *Orphan Drug Designations and Approvals List as of 03-03-2014*, HEALTH RES. & SERVS. ADMIN., <http://www.hrsa.gov/opa/programrequirements/orphandrugexclusion/orphandruglist.pdf> [hereinafter *Designations and Approvals List*]. Genentech has received 37 orphan designations and 15 approvals. *Id.*

<sup>130</sup> *Id.* Amgen has received 36 orphan designations and 10 approvals. *Id.*

<sup>131</sup> *Id.* Genzyme has received 39 orphan designations and 11 approvals. *Id.*

<sup>132</sup> Haffner et al., *supra* note 46, at 824 tbl. 1 (noting that in 2002, Genzyme Corporation had the most products with orphan designation, twelve; Amgen had eleven and Genentech had ten). Since a single product may have multiple orphan designations, Roche had the most orphan designations, twenty-two. *Id.* But only GlaxoSmithKline had ten orphan marketing approvals. *Id.*

<sup>133</sup> *Designations and Approvals List*, *supra* note 129. BioMarin has received nine orphan designations and three approvals. *Id.*

<sup>134</sup> See *About BioMarin*, BIOMARIN, <http://www.bmrn.com/about-us/index.php> (last visited Apr. 13, 2014); *Pipeline*, BIOMARIN, <http://bmrn.com/pipeline/> (last visited Apr. 13, 2014).

<sup>135</sup> OIG, ODA, *supra* note 65, at 9. Of note,

since 2010, orphan drugs have been partially exempted from the 340B Drug Pricing Program. Under the 340B Program, safety-net health care providers pay the same . . . discounted prices for drugs [paid by Medicaid programs]. The Patient Protection and Affordable Care Act expanded the list of entities eligible to participate in the 340B Program . . . Pursuant to section 204 of the Medicare and Medicaid Extenders Act, these newly-added entities are not entitled to pay the discounted 340B price for orphan drugs as long as those drugs are prescribed to treat the orphan diseases for which they were approved.

Greenwood, *supra* note 47, at 4. “A House Democrat who worked on the healthcare law said the situation had resulted from ‘an honest mistake in drafting,’ and he added, ‘No one intended to take away any of the drug discounts that children’s hospitals already had.’” Robert Pear, *Children’s Hospitals Lose Some Drug Discounts*, N.Y. TIMES, Dec. 7, 2010, at A18.

<sup>136</sup> OIG, ODA, *supra* note 65, at 13.

<sup>137</sup> Mark A. Rothstein & Phyllis Griffin Epps, *Ethical and Legal Implications of Pharmacogenomics*, 2 NATURE REVIEWS 228, 230 (2001); Pulsinelli, *supra* note 31, at 344.

scholar has urged no changes be made to the Act, in response to infrequent instances of perceived abuse, because of the legislation's unique success in achieving the desired result.<sup>138</sup>

Still, the ODA has not been without some controversy. In 1986, Amgen's first product, epoetin alfa (Epogen), received orphan designation and FDA approval to treat anemia associated with end-stage renal disease.<sup>139</sup> Whether by intentional business strategy or not, new off-label uses were subsequently identified for the product, as there were numerous foreseeable applications beyond end-stage renal disease. In fact, Epogen became the sixth best-selling drug in the U.S.<sup>140</sup> This method of seemingly arbitrary subdivision of a larger disease into smaller subgroups eligible for ODA incentives has been dubbed "salami slicing."<sup>141</sup> To prevent such behavior, the ODA formerly had required companies to demonstrate that a proffered subset was medically plausible.<sup>142</sup> As such, though the National Cancer Institute estimates that 921,780 people are currently living with melanoma in the U.S.,<sup>143</sup> the cancer has more than fifty orphan drug designations.<sup>144</sup> In 2011, the FDA published a proposed rule in response to confusion related to the meaning of a "medically plausible subset." Of the 324 requests for orphan-drug designation in 2010, 124 were denied or placed in abeyance pending response to deficiencies, and seventy-nine (64%) of those failed to identify an appropriate medically plausible subset of a population with a non-rare disease or condition.<sup>145</sup> BIO and others have long requested more guidance from the FDA as to how to define subsets, particularly those based on genetic profiles.

The final rule was published on June 12, 2013 and became effective August 12, 2013.<sup>146</sup> The FDA affirmed the effectiveness of the ODA as implemented:

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<sup>138</sup> Pulsinelli, *supra* note 31, at 345.

<sup>139</sup> *Search Orphan Drug and Designations*, U.S. FOOD & DRUG ADMIN., <http://fda.gov> (follow "For Industry" hyperlink; then follow "Developing Products for Rare Diseases & Conditions" hyperlink; then follow "Search Orphan Drug Designations and Approvals" hyperlink; then search "Epogen" in "Product Name"; then follow "Run Search" button; then follow "Row Num 1" hyperlink).

<sup>140</sup> *Sacrificing the Cash Cow*, 25 NATURE BIOTECHNOLOGY 363 (2007), available at <http://www.nature.com/nbt/journal/v25/n4/pdf/nbt0407-363.pdf>. Epogen, as of 2007, is the most successful biotech drug. *Id.* Three other instances are often cited as indicative of a windfall in profitability: AZT (initially only to treat AIDS but demonstrated benefit in HIV-positive patients as well); pentamidine isethionate (pneumonia associated with AIDS), and human growth hormone (hGH) (improper growth in children lacking the enzyme). Pulsinelli, *supra* note 31, at 316–17.

<sup>141</sup> Pulsinelli, *supra* note 31, at 315.

<sup>142</sup> David Loughnot, *Potential Interactions of the Orphan Drug Act and Pharmacogenomics: A Flood of Orphan Drugs and Abuses?*, 31 AM. J. L. & MED. 365, 374 (2005).

<sup>143</sup> *SEER Stat Fact Sheets: Melanoma of the Skin*, NAT'L CANCER INST., <http://seer.cancer.gov/statfacts/html/melan.html> (last visited Apr. 13, 2014).

<sup>144</sup> Meekings et al., *supra* note 51, at 664.

<sup>145</sup> Orphan Drug Regulations, *supra* note 67, at 35,130.

<sup>146</sup> *Id.* at 35,117.

FDA continues to believe that the current framework is the best means for giving effect to the intent of the Orphan Drug Act, to provide incentives for sponsors to develop promising drugs for rare diseases and conditions that would not otherwise be developed and approved, including drugs that are potentially safer and more effective than already approved drugs.<sup>147</sup>

Yet, in an effort to clarify misinterpretation surrounding the necessary demonstration required to establish an appropriate subgroup, the “medically plausible” language was stricken from the relevant regulation, in favor of the new definition of an orphan subset.<sup>148</sup> The FDA stressed that an orphan subset is a regulatory concept rather than a medical determination.<sup>149</sup> While not altering existing practice—the manner in which such subsets previously had been reviewed—the FDA announced that “eligibility for orphan subsets rests on whether use of the drug in a subset of persons with a non-rare disease or condition may be appropriate but use of the drug outside of that subset . . . would be inappropriate owing to some property(ies) of the drug.”<sup>150</sup> Therefore, an orphan subset cannot be considered without reference to the test article, irrespective of what medical science may suggest about the proffered insularity of the disease-state itself.

A comment expressed concern regarding the difficulty surrounding proof of a negative—a showing that the drug, in fact, was not suited for the wider disease population. The FDA responded, focusing on the affirmative evidence of effectiveness in the limited segment of the disease population and noting that the evidence need not necessarily rise to the level of “scientific proof.”<sup>151</sup> The FDA explicitly confirmed that orphan subsets may be informed by biomarkers and other targeted treatments.<sup>152</sup> The FDA, with BIO’s support, also explicitly affirmed that a drug that has demonstrated benefit in multiple rare

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<sup>147</sup> *Id.* at 35,122.

<sup>148</sup> *Id.* at 35,119.

<sup>149</sup> *Id.* (“It is intended to make clear to sponsors that an orphan subset is a regulatory concept specific to the Orphan Drug regulations, and that it does not simply mean any medically recognizable or clinically distinguishable subset of persons with a particular disease or condition.”).

<sup>150</sup> *Id.* at 35,119. The FDA identified three factors that may inform whether an appropriate subset exists: toxicity of the drug, mechanisms of drug action, and previous clinical experience. Whereas, clinical trial eligibility, the sponsor’s plan to study the drug for a select indication, the particular disease grade or stage, and price are not, by themselves, typically sufficient indicia to support orphan subsets. *Id.* at 35,120.

<sup>151</sup> *Id.* at 35,120.

<sup>152</sup> *Id.* at 35,121 (recognizing, by the FDA, that “orphan subsets may be predicated on biomarker-based and other targeted treatments as a principle for limiting the use of a drug to only a subset of patients with a non-rare disease or condition . . .”).

diseases may be eligible for multiple designations, even if the cumulative prevalence would exceed 200,000.<sup>153</sup> The FDA did recognize potential uncertainty regarding what constitutes a distinct disease and pointed to several factors to consider, including: pathogenesis, course of the disease, prognosis, and resistance to treatment.<sup>154</sup>

The FDA also expressed concern with the potential for “evergreening” or consecutive exclusivity periods for the same indication of the same drug without any meaningful benefit to the patient.<sup>155</sup> This concern centers primarily on the clinical superiority exception to orphan designation—such a showing required to prevent evergreening.<sup>156</sup> In rebuttal to the proposed rule, BIO first asserted that the FDA’s interpretation of clinical superiority unnecessarily conflates grant of the exclusivity period with orphan drug designation, the latter of which would entitle the company to the other development incentives.<sup>157</sup> BIO contended that allowing multiple designations in the same space would obviate the need for demonstrating clinical superiority—a difficult standard—and would result in more competition.<sup>158</sup> It is dubious to assume that, as a sound business model, companies would habitually enter an orphan market with an anticipated equivalent product and no opportunity to obtain market exclusivity.

BIO also expressed concern over the uncertainty of proof required to satisfy the “comparable” and “major contribution” components of clinical superiority because, at the time of the orphan designation request, it is often too early in the development process to speculate as to whether the molecule will have comparable efficacy and safety to an approved product.<sup>159</sup> BIO urged that “comparable efficacy and safety to an approved product should therefore not be used as a criterion for orphan designation.”<sup>160</sup> While considering the feasibility of a guidance document, the FDA rejected the comments advocating the elimination

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<sup>153</sup> *Id.* at 35,120 (“A drug that shows promise in multiple, different rare diseases or conditions may be eligible for multiple designations, one for each disease or condition, because FDA considers the prevalence within each disease or condition . . . even if the cumulative prevalence of all three diseases or conditions would exceed 200,000.”).

<sup>154</sup> *Id.* As an example, the FDA indicated that pneumonia in cystic fibrosis patients is considered to be distinct from community-acquired pneumonia when evaluating orphan drug designation. However, the FDA currently considers stage 1 breast cancer to be the same disease as stage 4 breast cancer. *Id.* The final rule points out the fluidity of these determinations based on the state of the science at the time of designation. *Id.* at 35,120–21.

<sup>155</sup> *Id.* at 35,127; see also Kate S. Gaudry, *Evergreening: A Common Practice to Protect New Drugs*, 29 NATURE BIOTECHNOLOGY 876 (2011).

<sup>156</sup> See 21 C.F.R. § 316.34(c) (2013).

<sup>157</sup> Letter from Biotechnology Industry Organization to the U.S. Food & Drug Administration, Comments on Proposed Rules related to “Orphan Drug Regulations” 2 (Jan. 17, 2012).

<sup>158</sup> *Id.*

<sup>159</sup> *Id.* at 6.

<sup>160</sup> *Id.*

of the requirement for a plausible hypothesis of clinical superiority when rendering the orphan designation determination.<sup>161</sup>

The final rule explains that the FDA interprets the FDCA to not permit orphan designation where there is an equivalent drug in the same space, approved for the same use.<sup>162</sup> The FDA clarified that a drug may still be considered clinically superior without demonstrating greater effectiveness or safety—though comparable—if it makes a “major contribution to patient care.”<sup>163</sup> For example, new dosage forms may be “clinically superior.”<sup>164</sup> The FDA confirmed that the same sponsor may receive market exclusivity upon showing clinical superiority to its own product.<sup>165</sup> The FDA also explained that a sponsor need not provide a plausible hypothesis of clinical superiority for a distinct subset, if another subset within the wider disease has already obtained orphan designation.<sup>166</sup> It was further emphasized that the grant of marketing exclusivity for an orphan drug must meet a higher bar; clinical superiority actually must be demonstrated.<sup>167</sup>

Last, and not surprisingly, the final rule does not address the cost of orphan products, which has left some patients without insurance coverage. For example, Oregon makes Medicaid coverage determinations essentially based on a health technology assessment,

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<sup>161</sup> Orphan Drug Regulations, *supra* note 67, at 35,122.

In the absence of a clinical superiority hypothesis, the Agency does not interpret the Orphan Drug regulations to permit designation of a drug that is otherwise the same as a drug that is already approved for the same use, regardless of whether the previously approved drug obtained orphan-drug designation or was eligible for orphan-drug exclusivity.

*Id.*

<sup>162</sup> *Id.*

<sup>163</sup> *Id.* at 35,123.

<sup>164</sup> *Id.* (“Some new dosage forms may be ‘clinically superior’ to previously approved dosage forms of the same drug under § 316.3(b)(3) and thus eligible for their own 7-year period of orphan exclusive approval.”).

<sup>165</sup> *Id.* at 35,122.

<sup>166</sup> *Id.* at 35,124.

If a drug is approved for only certain indications or uses within a rare disease or condition, a subsequent sponsor may obtain designation of the same drug for the remaining . . . indications or uses within the same rare disease or condition without having to provide a plausible hypothesis of clinical superiority over the already approved drug, provided the prevalence of the entire disease or condition remains under 200,000.

*Id.*

<sup>167</sup> *Id.* at 35,122 (“FDA advises sponsors that the clinical superiority requirements for orphan-drug designation and orphan-drug exclusivity are different: designation requires a plausible hypothesis of clinical superiority, exclusivity requires a demonstration of clinical superiority.”).

weighing cost with effectiveness.<sup>168</sup> Illustratively, “[t]he Commission reviewed the treatment of Hunter’s syndrome with enzyme replacement therapy and found it to have a minimal effect on the patient’s health at a cost of hundreds of thousands of dollars a year.”<sup>169</sup> As a result, such enzyme replacement therapies (“ERTs”) for rare diseases generally are not covered under Oregon’s Medicaid program, as they fall outside the current priority lines that demarcate coverage.<sup>170</sup>

## V. INTERNATIONAL TREATMENT OF ORPHAN DRUGS

The perceived success of the ODA has seen other countries adopt similar measures. Japan passed such legislation in 1993, and the European Union followed in 1999.<sup>171</sup> Briefly, by way of comparison, the term “drug gap” describes the difference in drugs approved in other jurisdictions, as compared to the U.S.<sup>172</sup> Such disparities result from differences in the definition of rarity—defined in the EU as less than five per 10,000 people.<sup>173</sup> There are also distinctions in the durations

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<sup>168</sup> See generally, Arti K. Rai, *Pharmacogenetic Interventions, Orphan Drugs, & Distributive Justice: The Role of Cost-Benefit Analysis*, 19 J. SOC. PHIL. & POL’Y 246, 254 (2001) (explaining a brief cost-benefit analysis).

<sup>169</sup> See OREGON HEALTH SERVS. COMM’N., *PRIORITIZATION OF HEALTH SERVICES* 26 (2009), available at <http://www.oregon.gov/oha/OHPR/HSC/docs/r/09hscbiennialreport.pdf>.

<sup>170</sup> See *Prioritized List of Human Services*, OREGON HEALTH PLAN 1.264, 684 (2013), <http://www.oregon.gov/oha/herc/PrioritizedList/10-1-2013%20Prioritized%20List%20of%20Health%20Services.pdf>. Oregon currently covers prioritized lines 1 – 498. *Id.* at GN-18. With the exception of infantile Pompe disease (line 264), ERT falls in line 684 (of 692 total lines). *Id.* Therefore, as a matter of budgetary constraint, this technology, though FDA approved, is generally unavailable through the Oregon Health Plan. *Id.*; AGENCY FOR HEALTHCARE RES. & QUALITY, *ENZYME-REPLACEMENT THERAPIES FOR LYSOSOMAL STORAGE DISEASES, EFFECTIVE HEALTH CARE PROGRAM* 12 (Jan. 2013), [www.ncbi.nlm.nih.gov/books/NBK117219/pdf/TOC.pdf](http://www.ncbi.nlm.nih.gov/books/NBK117219/pdf/TOC.pdf) [hereinafter *ERTS FOR LYSOSOMAL STORAGE DISEASES*]. There are, in fact, nine ERTs approved by the FDA for the treatment of rare diseases, as of January 2013. *Id.* tbl.1.

<sup>171</sup> Haffner et al., *supra* note 46, at 824. Singapore, Australia, Taiwan, South Korea, Hong Kong, South Africa, Turkey, and India also have orphan drug regimens. Aarti Sharma et al., *Orphan Drug: Development Trends and Strategies*, 2 J. PHARMACY & BIOALLIED SCI. 290 (2010), available at <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2996062/>. Canada hopes to soon adopt similar measures. *Id.*; *Harper Government Takes Action to Help Canadians with Rare Diseases—Launch of First Ever Canadian Framework to Increase Access to New Treatments and Information and Orphanet-Canada Online Portal*, ABOUT HEALTH CAN. (Oct. 3, 2012), [http://www.hc-sc.gc.ca/ahc-asc/media/nr-cpl/\\_2012/2012-147-eng.php](http://www.hc-sc.gc.ca/ahc-asc/media/nr-cpl/_2012/2012-147-eng.php) [hereinafter *Harper Government*]. At least one author has argued that Canada should not adopt a U.S.-based system. *Id.*; Matthew Herder, *When Everyone Is an Orphan: Against Adopting a U.S.-Styled Orphan Drug Policy in Canada*, 20 ACCOUNTABILITY IN RES.: POL’YS & QUALITY ASSURANCE 227 (2013).

<sup>172</sup> See *Drug Lag & Drug Loss, Glossary*, INDEP. INST., [http://www.fda.gov/glossary.shtml#drug\\_lag](http://www.fda.gov/glossary.shtml#drug_lag) (last visited Apr. 13, 2014); John Matthews & Lucas Glass, *The Effect of Market-Based Economic Factors on the Adoption of Orphan Drugs Across Multiple Countries*, 47 THERAPEUTIC INNOVATION & REG. SCI. 226 (2013).

<sup>173</sup> Sharma et al., *supra* note 171.



of market exclusivity, with Japan providing ten years and Australia allowing five years.<sup>174</sup> Of note, a “clawback” provision exists in the EU version that permits a reduction in the statutory exclusivity period if the orphan drug becomes sufficiently profitable within the protected time; it has never been used.<sup>175</sup>

Greater harmonization across borders has been recommended.<sup>176</sup> Since both the European Medicines Agency (“EMA”) and the FDA require submission of annual reports after orphan drug designation but prior to marketing approval, an optional process was announced in 2010, which allows for a single filing.<sup>177</sup> The concerted inter-agency collaboration may portend or warrant defining the relevant market beyond merely those affected with a particular condition in the U.S. but, rather, by reference to every jurisdiction in which the manufacturer seeks to enter the market. Interestingly, many of the highly prevalent infectious diseases endemic to developing nations have been reduced to rare disease prevalence in the U.S. and, therefore, are eligible for orphan designation. In this way, the first- and second-line anti-tuberculosis drugs rifampin and rifapentine received orphan designation, yet have significant world-wide applicability.<sup>178</sup> In essence, this would keep the U.S. from subsidizing the cost of drugs in countries where price controls limit the amount that can be charged. However, such a process would prove unwieldy and ignores social and distributive justice considerations by potentially restricting dispersion of life-saving therapies.

## VI. REPURPOSED MOLECULES

It has been argued that the ODA has successfully revived previously discarded treatments.<sup>179</sup> Illustratively, despite the teratogenic effects that resulted in the 1960s when the sedative was prescribed in Europe for nausea associated with pregnancy, thalidomide received FDA approval in 2006 as an orphan drug for the treatment of multiple myeloma, after receiving initial approval in the

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<sup>174</sup> *Id.* tbl.4.

<sup>175</sup> P.M. Barrett et al., *Cystic Fibrosis in an Era of Genomically Guided Therapy*, 21 HUMAN MOLECULAR GENETICS R66, R70 (Oct. 15, 2012), available at <http://hmg.oxfordjournals.org/content/early/2012/09/17/hmg.dds345.full.pdf>; see also Greenwood, *supra* note 47, at 10.

<sup>176</sup> See Wellman-Labadie & Zhou, *supra* note 50, at 221.

<sup>177</sup> Press Release, European Meds. Agency, FDA & EMA Agree to Accept a Single Orphan Drug Designation Annual Report 1 (Feb. 26, 2010), available at [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Press\\_release/2010/03/WC500074890.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2010/03/WC500074890.pdf).

<sup>178</sup> Maher & Haffner, *supra* note 99, at 76.

<sup>179</sup> Wellman-Labadie & Zhou, *supra* note 50, at 226. A 2010 study identified 26 discontinued products that later received orphan designation, 14 of which ultimately received market approval (including Vioxx). *Id.*

U.S. for the treatment of leprosy.<sup>180</sup> “Repurposing” generally refers to studying a small molecule or a biologic approved by the FDA to treat one disease or condition to see if it is safe and effective for treating other diseases.<sup>181</sup>

There are many different strategies for repurposing molecules and many players in the space.<sup>182</sup> The NIH’s National Center for Advancing Translational Sciences (“NCATS”) implemented a program in May 2012, titled Discovering New Therapeutic Uses for Existing Molecules (“DNTUEM”).<sup>183</sup> NCATS oversees a program designed specifically for rare diseases, Therapeutics for Rare and Neglected Diseases (“TRND”). Additionally, the FDA created a database of known molecular targets, the Rare Diseases Repurposing Database (“RDRD”), which indexes orphan designations and approvals.<sup>184</sup> The private sector has also taken notice. Pfizer partnered with Washington University to reposition off-patent products and, also, has established an internal Indication Discovery Unit (“IDU”) to reposition underutilized assets.<sup>185</sup> GlaxoSmithKline has made available approximately 500 patents to a patent pool.<sup>186</sup> Also, Gilead has made

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<sup>180</sup> *Thalidomide (marketed as Thalomid) Information*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm107296.htm> (last visited Apr. 13, 2014) [hereinafter *Thalidomide Information*]; see also *Significant Dates in U.S. Food and Drug Law History*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/aboutfda/whatwedo/history/milestones/ucm128305.htm> (last visited Apr. 13, 2013).

<sup>181</sup> *Rescuing and Repurposing Drugs*, NAT’L CTR. FOR ADVANCING TRANSLATIONAL SCI., <http://www.ncats.nih.gov/research/reengineering/rescue-repurpose/rescue-repurpose.html> (last visited Oct. 15, 2013). This is distinguished from drug “rescue,” which refers to research using small molecules and biologics that previously were used in studies but not further developed and submitted for FDA approval. *Id.*; Sheryl G. Stolberg, *Thalidomide Approved to Treat Leprosy, With Other Uses Seen*, N.Y. TIMES, July 17, 1998, <http://www.nytimes.com/1998/07/17/us/thalidomide-approved-to-treat-leprosy-with-other-uses-seen.html>. Illustratively, having never received approval in the U.S., thalidomide was approved for the treatment of leprosy in 1998. *Id.*; see also *Thalidomide Information*, *supra* note 180.

<sup>182</sup> See generally Ramaiah Muthyala, *Orphan/rare drug discovery through drug repositioning*, 8 DRUG DISCOVERY TODAY: THERAPEUTIC STRATEGIES 71, 72 (2011).

<sup>183</sup> *Discovering New Therapeutic Uses for Existing Molecules*, NAT’L CTR. FOR ADVANCING TRANSLATIONAL SCIENCES, <http://www.ncats.nih.gov/research/reengineering/rescue-repurpose/therapeutic-uses/therapeutic-uses.html> (last visited Apr. 13, 2014). Numerous pharmaceutical companies provided 58 compounds to the program and, in June 2013, NIH awarded \$12.7 million to fund nine projects. *Id.*; Ann M. Thayer, *Drug Repurposing*, 90 CHEMICAL & ENG’G NEWS 15 (2012), available at <http://cen.acs.org/articles/90/i40/Drug-Repurposing.html?h=1031248274> (“The NCATS program has garnered praise but also debate. One issue is around government support of corporate product development. In the program, a research partner will own new intellectual property (IP) that it generates, but the company that owns the compound will have the first right to develop it.”).

<sup>184</sup> See generally Muthyala, *supra* note 182, at 73; see also *A Valuable Resource for Drug Developers: The Rare Disease Repurposing Database (RDRD)*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/HowtoapplyforOrphanProductDesignation/ucm216147.htm> (last updated June 17, 2013).

<sup>185</sup> Muthyala, *supra* note 182, at 74.

<sup>186</sup> *Id.*

available medicines through voluntary licensing for research into the possibility of repositioning.<sup>187</sup>

Exploring the utility of repositioning, a consultant concluded that “the identification of common mechanism of action that allow repositioning from one indication to another are attractive.”<sup>188</sup> In addition to the stockpile of chemical entities (estimated to be 9,000 compounds<sup>189</sup>), it is also estimated that the well of unsuccessful drug candidates increases at the rate of 150 to 200 compounds per year.<sup>190</sup> Drug repositioning was “expected to generate up to \$20 billion in annual sales in 2012.”<sup>191</sup> In addition to this value, drug repositioning has a number of R&D advantages including: reduced research and development (R&D) timelines by up to three to five years, reduced development cost (due to the likely availability of clinical safety, toleration, and efficacy data), and improved probability of success.<sup>192</sup> Thompson Reuters estimates a 15% increase in rate of success for bringing products to market from Phase II and III trials, as compared to new molecular entities; the rates for repurposed compounds are 25% and 65%, respectively.<sup>193</sup> The RDRD lists 236 repurposed products with orphan designation and 127 compounds with marketing approval.<sup>194</sup> Thus, repurposing has become a prominent drug development strategy, particularly with advances in bioinformatics.

Of course, the strategy is not without risk. Problematically, a product that moves from a common to an orphan disease may incur lower production costs, but a sponsor may find it difficult to recoup the costs of the clinical trials in the new indication, due to the existing prices of the originator.<sup>195</sup> Also, there is a significant likelihood for physicians to prescribe the cheaper original brand or generic instead of the newly developed orphan drug.<sup>196</sup> Due to substantial price

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<sup>187</sup> *Id.*

<sup>188</sup> Caroline Mathie, *Orphan Drug Repositioning—To or From a More Common Disease?*, PHARMAPHORUM (Feb. 4, 2013), <http://www.pharmaphorum.com/articles/orphan-drug-repositioning-%E2%80%93-to-or-from-a-more-common-disease> (noting the examples Sutent and Gleevec, for which the indications expanded beyond the original orphan diseases of renal cell carcinoma and CML, respectively).

<sup>189</sup> Muthyala, *supra* note 182, at 72.

<sup>190</sup> *Id.*; see also JOHN ARROWSMITH & RICHARD HARRISON, DRUG REPOSITIONING: BRINGING NEW LIFE TO SHELVED ASSETS & EXISTING DRUGS 19 (Michael J. Barratt eds., 1st ed. 2012), available at [http://media.johnwiley.com.au/product\\_data/excerpt/74/04708782/0470878274-101.pdf](http://media.johnwiley.com.au/product_data/excerpt/74/04708782/0470878274-101.pdf).

<sup>191</sup> THOMSON REUTERS, KNOWLEDGE-BASED DRUG REPOSITIONING TO DRIVE R&D PRODUCTIVITY 1 (2012), available at <http://thomsonreuters.com/business-unit/science/subsector/pdf/knowledge-based-drug-repositioning-to-drive-rd-productivity.pdf> (citing Tobinick E.L., *The Value of Drug Repositioning in the Current Pharmaceutical Market*, 22 DRUG NEWS & PERSPS. 119 (2009)).

<sup>192</sup> *Id.* (citing Ted T. Ashburn et al., *Drug Repositioning: Identifying and Developing New Uses For Existing Drugs*, 8 NATURE REV. 673 (2004)).

<sup>193</sup> *Id.* fig.1.

<sup>194</sup> Muthyala, *supra* note 182, at 74.

<sup>195</sup> Mathie, *supra* note 188.

<sup>196</sup> *Id.*

increases in just such situations, recent disputes have garnered much publicity concerning the ODA's application to repurposed molecules or, for the purpose of this paper, drugs available to patients prior to orphan designation and FDA approval for marketing as such. Two detailed case studies follow.

### A. Case Study: Makena® and KV Pharmaceuticals

First approved in 1956 under the trade name Delalutin, 17 $\alpha$ -hydroxyprogesterone caproate ("17P"), was indicated for the treatment of gynecological conditions, such as uterine adenocarcinoma and menorrhagia.<sup>197</sup> In 1999, Bristol-Myers Squibb requested and the FDA granted withdrawal of its market approval for Delalutin.<sup>198</sup> In 2003, a seminal study demonstrated the clinical effectiveness of 17P in preventing premature birth in pregnant women with a history of spontaneous preterm delivery.<sup>199</sup> The recommendation was adopted by the American College of Obstetricians and Gynecologists ("ACOG"), and the use of 17P became the standard of care by 2005.<sup>200</sup> Seventeen alpha-hydroxyprogesterone caproate is the dominant treatment to prevent preterm birth in pregnant woman with a history of preterm delivery; there are no other available treatments.<sup>201</sup> Since 17P had never been approved for this use and it was no longer commercially available, prescriptions were filled for the sterile injectable through compounding pharmacies.<sup>202</sup> The price of compounded 17P was \$15 per injection, for a cost per pregnancy of approximately \$315.<sup>203</sup>

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<sup>197</sup> Determination that Delalutin Injection, 125 mg/ml and 25 mg/ml, Was Not Withdrawn from Sale for Reasons of Safety or Effectiveness, 75 Fed. Reg. 36,419, 36,419 (June 25, 2010), <http://www.gpo.gov/fdsys/pkg/FR-2010-06-25/html/2010-15416.htm> [hereinafter Delalutin Injection]; see also Greenwood, *supra* note 47, at 7.

<sup>198</sup> Greenwood, *supra* note 47, at 7.

<sup>199</sup> Paul J. Meis et al., *Prevention of Recurrent Preterm Delivery by 17 Alpha-Hydroxyprogesterone Caproate*, 348 NEW ENG. J. MED. 2379, 2739 (2003), available at <http://www.nejm.org/doi/pdf/10.1056/NEJMoa035140>.

<sup>200</sup> Michelle Oxman, *What Does the Makena Story Tell Us About the Orphan Drug Act?*, WOLTERS KLUWER L. & HEALTH (Sept. 24, 2012), <http://health.wolterskluwerlb.com/2012/09/what-does-the-makena-story-tell-us-about-the-orphan-drug-act/>.

<sup>201</sup> A.O. Odibo et al., *17 $\alpha$ -hydroxyprogesterone Caproate for the Prevention of Preterm Delivery: A Cost-Effectiveness Analysis*, 108 J. OF OBSTETRICS & GYNACOLOGY RES. 492 (2006).

<sup>202</sup> Yesha Patel & Martha M. Rumore, *Hydroxyprogesterone Caproate Injection (Makena) One Year Later*, 37 PHARMACY & THERAPEUTICS 405, 405 (2012). In light of recent events involving tainted sterile injectables from compounding pharmacies in Massachusetts and Georgia, the question about the benefits of FDA approval and current Good Manufacturing Practices (cGMPs) are particularly *apropos*, having wider implications for product consistency assumptions between state-regulated compounding pharmacies and FDA-regulated manufacturers. Scott Gottlieb, *Compounding a Crisis at FDA*, FORBES (May 24, 2013, 8:59 A.M.), <http://www.forbes.com/sites/scottgottlieb/2013/05/24/compounding-a-crisis-at-fda/>. New legislation should grant the FDA more authority over large-scale compounding. *Id.*

<sup>203</sup> Patel & Rumore, *supra* note 202, at 406.

On May 6, 2006, KV Pharmaceutical (“KV”)<sup>204</sup> submitted a NDA seeking approval to market 17P for “women with a singleton pregnancy and a history of preterm birth, to reduce the risk of another preterm birth.”<sup>205</sup> It was estimated that approximately 150,000 pregnant women per year present with a prior preterm delivery.<sup>206</sup> The drug received orphan drug designation on January 5, 2007 and was approved for marketing, under the trade name Makena, on February 3, 2011.<sup>207</sup> Also on February 3, 2011, the FDA denied a citizen petition from the Sidelines National Support Network, seeking revocation of Makena’s orphan-drug designation.<sup>208</sup>

Both the compounded and branded products contain the same active ingredients suspended in castor oil and are administered prophylactically in weekly 250mg doses, via intramuscular injection, commencing at sixteen weeks of gestation and continuing through week thirty-six or delivery, whichever occurs first.<sup>209</sup> At the urging of KV, the FDA investigated claims that compounded products were impure and not potent, ultimately declining to make such a categorical determination.<sup>210</sup> However, of note, there is some indication that 17P was not utilized as pervasively as it might otherwise have been if marketed by a pharmaceutical company.<sup>211</sup> KV set the price of the

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<sup>204</sup> KV Pharmaceutical had a significant history of noncompliance, including violation of good manufacturing practices and distribution of misbranded and adulterated drugs, which was followed by both a de-listing warning from the NYSE due to falling stock price and a securities fraud action brought by a class of investors. See Oxman, *supra* note 200; *United States v. KV Pharm. Co.*, No. 4:09 CV 334 RWS, ¶ 3 (E.D. Mo. Mar. 6, 2009), available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/Selecte dEnforcementActionsonUnapprovedDrugs/UCM245157.pdf>; Nate Raymond, *U.S. Court Revives KV Pharmaceutical Investor Suit*, REUTERS (June 4, 2012, 5:23 P.M.), <http://www.reuters.com/article/2012/06/04/us-kvpharmaceutical-investors-idUSBRE85312N20120604>; *Pub. Pension Fund Grp. v. KV Pharm. Co.*, No. 4:08-CV-1859 (CEJ), 2013 WL 1293816, at \*1 (E.D. Mo. Mar. 28, 2013).

<sup>205</sup> Greenwood, *supra* note 47, at 7.

<sup>206</sup> Oxman, *supra* note 200.

<sup>207</sup> *Makena Results, Search Orphan Drug Designations and Approvals*, U.S. FOOD & DRUG ADMIN., [http://www.accessdata.fda.gov/scripts/opdlisting/oopd/OOPD\\_Results\\_2.cfm?Index\\_Number=218706](http://www.accessdata.fda.gov/scripts/opdlisting/oopd/OOPD_Results_2.cfm?Index_Number=218706) (last visited Mar. 7, 2014).

<sup>208</sup> Letter from Leslie Kux, Acting Assistant Comm’r for Policy, U.S. Food and Drug Admin., to Candace Hurley, Exec. Director, Sidelines Nat’l Support Network 1 (Feb. 3, 2011), available at <http://www.regulations.gov/contentStreamer?objectId=0900006480e6e38c&disposition=attachment&contentType=pdf>; Greenwood, *supra* note 47, at 7. Sidelines National Support Network is “a non-profit organization providing international support for women and their families experiencing complicated pregnancies and premature births.” Greenwood, *supra* note 47, at 7.

<sup>209</sup> Patel & Rumore, *supra* note 202, at 405, 407.

<sup>210</sup> *Updated FDA Statement on Compounded Versions of hydroxyprogesterone caproate (the active ingredient in Makena)*, U.S. FOOD & DRUG ADMIN. (June 15, 2012), <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm308546.htm>. Finding sub-optimal potency in a small percentage of those tested, the FDA stated: “[a]lthough the analysis of this limited sample of compounded hydroxyprogesterone caproate products and APIs did not identify any major safety problems, approved drug products, such as Makena, provide a greater assurance of safety and effectiveness than do compounded products.” *Id.*

<sup>211</sup> Greenwood, *supra* note 47, at 14.

drug at \$1,440 per injection, for a cost per pregnancy of approximately \$30,240.<sup>212</sup> As a result of the cost, Senator Sherrod Brown (D-OH) wrote to KV requesting reconsideration of the “massive” price increase, and, on March 17, 2011, questioned FDA Commissioner Margaret Hamburg on the subject.<sup>213</sup> Also on that day, Senators Brown and Klobuchar (D-MN) sent a letter to FTC Chair Jon Leibowitz alleging anti-competitive behavior in the pricing structure.<sup>214</sup>

The outcry over the cost of Makena intensified because the drug’s sponsor relied on government-funded research to obtain FDA approval (such funding unrelated to the research tax credit associated with the ODA).<sup>215</sup> Reimbursing a manufacturer for research costs paid for through initial public investment remains controversial.<sup>216</sup> On March 30, 2011, the FDA issued a press release in which it explained, “KV Pharmaceuticals, the drug’s owner, received considerable assistance from the federal government in connection with the development of Makena by relying on research funded by the National Institutes of Health to demonstrate the drug’s effectiveness.”<sup>217</sup> The agency concluded:

In order to support access to this important drug, at this time and under this unique situation, FDA does not intend to take enforcement action against pharmacies that compound hydroxyprogesterone caproate based on a valid prescription for an individually identified patient unless the compounded products are unsafe, of substandard quality, or are not being compounded in accordance with appropriate standards for compounding sterile products. As always, FDA may at any time revisit a decision to exercise enforcement discretion.<sup>218</sup>

On March 30, 2011, the Centers for Medicare & Medicaid Services (“CMS”) issued a statement announcing that compounded 17P could be

<sup>212</sup> *Id.* at 8.

<sup>213</sup> Letter from Sherrod Brown, U.S. Senate, to Greg Divis, Chief Exec. Officer, KV Pharm. Co. (Mar. 10, 2011), available at <http://www.brown.senate.gov/imo/media/doc/Makena%20Letter.pdf>; *Brown to Grill FDA Commissioner on Massive Price Increase for Drug that Prevents Premature Labor*, SHERROD BROWN SEN. FOR OHIO (Mar. 17, 2011), <http://www.brown.senate.gov/newsroom/press/release/brown-to-grill-fda-commissioner-on-massive-price-increase-for-drug-that-prevents-premature-labor>.

<sup>214</sup> Greenwood, *supra* note 47, at 8 n.40; Letter from Sherrod Brown & Amy Klobuchar to the Honorable Jon Leibowitz, Chairman, Fed. Trade Comm’n, PROJECT VOTE SMART (Mar. 17, 2011), <http://votesmart.org/public-statement/595790/#.UrPE1vSrxDg>.

<sup>215</sup> Greenwood, *supra* note 47, at 8. KV contends that those funds amounted to only a small percent of the total development expenditure. *Id.* at 8 n.41.

<sup>216</sup> Aaron S. Kesselheim et al., *The Prevalence and Cost of Unapproved Uses of Top-selling Orphan Drugs*, 7 PLOS ONE e31894, at \*7 (2012).

<sup>217</sup> *FDA Statement on Makena*, U.S. FOOD & DRUG ADMIN. (Mar. 30, 2011), <http://www.fda.gov/newsEvents/Newsroom/PressAnnouncements/ucm249025.htm>.

<sup>218</sup> *Id.*

reimbursed by Medicaid, providing coverage guidance to states, and recommending the International Academy of Compounding Pharmacists locator service.<sup>219</sup> On July 5, 2012, KV filed suit, “challenging the FDA’s decision to decline to take enforcement action against pharmacies that compound 17P.”<sup>220</sup> The court declined to exercise jurisdiction over an FDA press release.<sup>221</sup> KV did initiate successful litigation against numerous states to ensure coverage.<sup>222</sup>

Confronted with the availability of compounded 17P and Makena, payers have adopted every possible reimbursement approach. Currently, formularies cover: (1) compounded 17P only; (2) Makena with step therapy, requiring that compounded 17P be used first; (3) Makena and 17P; or (4) Makena only.<sup>223</sup> Due to insufficient data to support the compounded product and additional inherent compounding risks, Oregon Health Authority prefers the branded product over the compounded product.<sup>224</sup> United Healthcare supports the physician’s discretion to use compounded preservative-free 17P, if the prescribing practitioner has determined that a compounded product is necessary for the particular patient and would provide a significant difference for

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<sup>219</sup> Greenwood, *supra* note 47, at 9; *see also* Letter from Cindy Mann, Director, Ctr. for Medicaid, CHIP & Survey & Certification (CMCS), to States (Mar. 30, 2011), *available at* <http://downloads.cms.gov/cmsgov/archived-downloads/CMCSBulletins/downloads/Makena-CMCS-Info-Bulletin-03-30-2011.pdf>.

<sup>220</sup> Greenwood, *supra* note 47, at 9.

<sup>221</sup> *K-V Pharm. Co. v. U.S. Food & Drug Admin.*, 889 F. Supp. 2d 119, 133 (2012). On September 6, 2012, the District Court granted the FDA’s motion to dismiss for failure to state a claim, “finding that the FDA’s issuance of the Press Release was an unreviewable action.” Greenwood, *supra* note 47, at 9. KV appealed, averring:

“[n]ever before has FDA publicly authorized and encouraged compounders to produce and distribute nationwide unapproved, uncustomized drugs to replace an FDA-approved drug” and arguing that “the statutory and regulatory restrictions on compounding serve important patient-safety goals because only approved drugs have been shown to be effective and safe in clinical trials, are manufactured under strict FDA-approved controls, have FDA-approved labeling, and are subject to FDA’s post-approval requirements and oversight.”

*Id.* at 9–10.

<sup>222</sup> Ed Silverman, *KV Pharma Finally Wins a Victory, For Now*, FORBES (Aug. 13, 2012, 1:06 P.M.), <http://www.forbes.com/sites/edsilverman/2012/08/13/kv-pharma-finally-wins-a-victory-for-now/>; Jim Doyle, *KV Pharmaceutical Suing for Survival*, ST. LOUIS POST-DISPATCH (Sept. 2, 2012, 12:15 A.M.), [http://www.stltoday.com/business/local/kv-pharmaceutical-suing-for-survival/article\\_098f5b0c-f3a6-11e1-bad1-001a4bcf6878.html](http://www.stltoday.com/business/local/kv-pharmaceutical-suing-for-survival/article_098f5b0c-f3a6-11e1-bad1-001a4bcf6878.html).

<sup>223</sup> Patel & Rumore, *supra* note 202, at 408.

<sup>224</sup> *See Oregon Health Plan Policies, Rules and Guidelines: Clinical Information*, OREGON HEALTH AUTH., <http://www.dhs.state.or.us/policy/healthplan/guides/pharmacy/clinical.html> (last visited Mar. 8, 2014); Brandy Fouts, *Drug Use Evaluation: 17 alpha-hydroxyprogesterone caproate*, OR. STATE UNIV. COLL. OF PHARMACY (May 2013), [http://pharmacy.oregonstate.edu/drug\\_policy/sites/default/files/pages/dur\\_board/evaluations/articles/2013\\_05\\_30\\_Makena\\_NDE.pdf](http://pharmacy.oregonstate.edu/drug_policy/sites/default/files/pages/dur_board/evaluations/articles/2013_05_30_Makena_NDE.pdf).

the patient as compared to the FDA-approved commercially available drug product, Makena.<sup>225</sup>

KV Pharmaceuticals may soon face additional competition in the market. After seeking a declaration that Delalutin was not withdrawn for safety or efficacy concerns,<sup>226</sup> McGuff Pharmaceuticals submitted an ANDA, intending to market a generic version of Delalutin.<sup>227</sup> KV Pharmaceutical filed a petition with the FDA in June 2012, urging the FDA not to approve the application as a violation of the exclusive marketing rights for Makena.<sup>228</sup> The FDA rejected the petition:

FDA's approval of an ANDA for a generic version of Delalutin would not violate Makena's orphan-drug exclusivity because orphan-drug exclusivity applies only to the indication for which the orphan drug has been designated and approved. In other words, should FDA approve an ANDA referencing Delalutin as the RLD, FDA will not be approving a drug application proposing the same drug and the same use as Makena.<sup>229</sup>

In response to the competition, KV eventually announced that it had decided to reduce the list price of Makena by approximately 50% to \$690, or \$14,490 for the standard twenty-one doses, and to expand patient financial assistance.<sup>230</sup> On August 4, 2012, KV filed voluntary Chapter 11 bankruptcy, in light of the competition from compounding pharmacies.<sup>231</sup> Ultimately, by not fully enforcing the ODA's seven-year

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<sup>225</sup> See *Updated Information about 17 Alpha-Hydroxyprogesterone Caproate (17P) Injection*, UNITED HEALTHCARE 2, [https://www.unitedhealthcareonline.com/ccmcontent/ProviderII/UHC/en-US/Assets/ProviderStaticFiles/ProviderStaticFilesPdf/Clinician%20Resources/Womens%20Health/Makena\\_17P\\_Overview.pdf](https://www.unitedhealthcareonline.com/ccmcontent/ProviderII/UHC/en-US/Assets/ProviderStaticFiles/ProviderStaticFilesPdf/Clinician%20Resources/Womens%20Health/Makena_17P_Overview.pdf) (last visited Mar. 8, 2014).

<sup>226</sup> Delalutin Injection, *supra* note 197, at 36,419. Note that while current safety and effectiveness data are considered, current standard of care does not play a role in such analysis. Letter from Janet Woodcock, Director, Ctr. for Drug Evaluation & Res., U.S. Food & Drug Admin., to Michael J. Jozwiakowski, Vice President, KV Pharm. Co. 8 (Jan. 2, 2013), *available at* <http://www.regulations.gov/contentStreamer?objectId=09000064811a56b7&disposition=attachment&contentType=pdf> [hereinafter Letter from Woodcock].

<sup>227</sup> Letter from Ronald M. McGuff, President/CEO, McGuff Pharm. Inc., to U.S. Food & Drug Admin. 1 (Sept. 19, 2012).

<sup>228</sup> Letter from Gregory J. Divis, President/CEO, KV Pharm. Co., to U.S. Food & Drug Admin. 1 (Nov. 12, 2012), *available at* <http://www.regulations.gov/api/contentStreamer?objectId=090000648116f3d3&disposition=attachment&contentType=pdf>.

<sup>229</sup> Silverman, *supra* note 222; *see also* Letter from Woodcock, *supra* note 226. The Fourth Circuit foreclosed a foreseeable intended use theory, asserting that “a foreseeable off-label use [theory] to bar the approval of generic drugs, even for unprotected indications . . . [would add] a huge evidentiary hurdle to the generic drug approval process [and] would be profoundly anticompetitive.” *Id.* at 7 (citing *Sigma-Tau Pharms. Inc. v. Schwetz*, 288 F.3d 141, 145 (4th Cir. 2002)). This scenario clearly illustrates the advantage of a drug substance patent over market exclusivity. *Id.*

<sup>230</sup> Greenwood, *supra* note 47, at 9.

<sup>231</sup> *Id.*



exclusivity period, the FDA preserved affordability.<sup>232</sup> In so doing, the agency undermined sponsor expectation with significant economic fallout, invited litigation, and fanned the flames of debate concerning the appropriate balance between incentivizing research and ensuring access to the fruits of that innovation.

### *B. Case Study: H.P. Acthar® Gel and Questcor Pharmaceutical*

H.P. Acthar Gel stands as another example of a repurposed molecule, a previously available drug awarded orphan designation for a new indication, only to result in a significant price increase. It also demonstrates that—though possibly infrequent—the strategy employed by KV Pharmaceuticals is not an isolated occurrence. The adrenocorticotrophic hormone or ACTH, a biologic, was developed by a division of Armour & Company, a meatpacking company, in conjunction with Nobel Laureate researchers at the Mayo Clinic.<sup>233</sup> The FDA approved the biologic to treat multiple sclerosis and other indications in 1952.<sup>234</sup> In 1995, Rhône-Poulenc, which became Aventis and eventually merged with Sanofi, opted to discontinue production rather than invest in manufacturing improvements required by the FDA as a result of numerous quality control problems.<sup>235</sup> However, a limited supply was rationed to treat only infantile spasms (also known as West syndrome, a rare and potentially fatal epileptic disorder with an onset generally before the age of one) or severe flare-ups of multiple sclerosis, with the company losing several million dollars a year on the biologic.<sup>236</sup>

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<sup>232</sup> *Id.* at 14. Interestingly, on August 8, 2012, the FDA, for the first time, revoked the exclusivity period conferred to an orphan drug. Letter from Leslie Kux, Assistant Comm. For Policy, U.S. Food and Drug Admin. to Peter Turner, President, CSL Behring 1–2 (Aug. 8, 2012), available at <http://www.regulations.gov/contentStreamer?objectId=09000064810c8c71&disposition=attachment&contentType=pdf>. The biologic, Wilate, is manufactured by Octapharma and used to treat bleeding associated with von Willebrand disease. *Id.* at 5. In response to a citizen petition and though the FDA had originally found it hypothetically plausible that Wilate was superior to Humate-P, the FDA reversed its prior decision. *Id.* at 1–2, 16. However, the FDA determined that Wilate could retain the orphan designation because it had shown a hypothetical plausibility at the time of submission of the application—after all, the FDA believed the evidence to satisfy the standard on first blush. *Id.* at 5–6.

<sup>233</sup> Andrew Pollack, *Finding Profits, at \$28,000 a Vial*, N.Y. TIMES, Dec. 30, 2012, at BU1, available at <http://www.nytimes.com/2012/12/30/business/questcor-finds-profit-for-acthar-drug-at-28000-a-vial.html?pagewanted=all>.

<sup>234</sup> Samson, *supra* note 72, at A14. Other estimates place the pre-2007 cost of Acthar at \$2,062.79 per vial. Jacob Gettig et al., *H.P. Acthar Gel and Cosyntropin Review: Clinical and Financial Implications*, 34 PHARMACY & THERAPEUTICS 250, 250 (2009), available at [http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2697107/pdf/ptj34\\_5p250.pdf](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2697107/pdf/ptj34_5p250.pdf).

<sup>235</sup> Pollack, *supra* note 233.

<sup>236</sup> *Id.*

Questcor Pharmaceutical bought the rights to the biologic from its previous owner for \$100,000 in 2001 (as well as a 1% royalty on annual sales over \$10 million) and immediately raised the price of H.P. Acthar Gel from a reported low of \$40 a vial.<sup>237</sup> In 2003, while widely prescribed for this purpose, H.P. Acthar Gel, one of only the company's few products, received designation as an orphan drug for the treatment of infantile spasms, with an estimated prevalence of 2,000 individuals.<sup>238</sup> Although sales of H.P. Acthar Gel totaled \$12 million per year by 2006, the company remained unprofitable.<sup>239</sup> Consequently, without a diverse product portfolio, Questcor began selling a vial for \$28,000 in 2007, amounting to approximately \$150,000 per regimen.<sup>240</sup> Then, in July 2008, the U.S. Senate Joint Economic Committee held a special hearing, titled "Small Market Drugs, Big Price Tags: Are Drug Companies Exploiting People with Rare Disease?"<sup>241</sup> Senator Schumer began the hearing, stating:

One might[] say that a brand new drug that just hit the market might be pricey because it had to recoup research and development expenditures, but Acthar has been on the market for three decades. . . . Our witnesses today are going to shine a light on practices that look uncomfortably like an abuse of the pricing power we give to drug companies. In case after case, it appears that PHARMA companies have been taking critical drugs that have been on the market for years—with the costs of their development long since paid for—and increasing prices to the very highest levels the market will bear.<sup>242</sup>

Testimony described substantial drug pricing increases, as much as by 3,436% in one instance.<sup>243</sup> After rejection of its first attempt, Questcor finally received both marketing approval for the biologic in connection with the treatment of infantile spasms and marketing exclusivity in 2010.<sup>244</sup>

However, there is evidence that H.P. Acthar Gel might not be the most cost-effective treatment. It has been reported that studies

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<sup>237</sup> *Id.*

<sup>238</sup> Samson, *supra* note 72, at A14.

<sup>239</sup> Pollack, *supra* note 233. While complex, manufacturing accounts for approximately one cent of every dollar that Questcor charges for Acthar. *Id.*

<sup>240</sup> *Id.*

<sup>241</sup> *Small Market Drugs, Big Price Tags: Are Drug Companies Exploiting People with Rare Disease?: Hearing Before the Joint Economic Comm.*, 110th Cong. 1–37 (2008).

<sup>242</sup> *Id.* at 6 (statement of Charles E. Schumer, U.S. Sen. N.Y.).

<sup>243</sup> *Id.* at 31 (statement of Madeline Carpinelli, Res. fellow & Stephen W. Schondelmeyer, Professor and Dir., Prime Inst., Coll. of Pharmacy, Univ. of Minn.).

<sup>244</sup> See *Search Orphan Drug Designations and Approvals*, U.S. FOOD & DRUG ADMIN., [http://www.accessdata.fda.gov/scripts/opdlisting/oopd/OOPD\\_Results\\_2.cfm?Index\\_Number=168103](http://www.accessdata.fda.gov/scripts/opdlisting/oopd/OOPD_Results_2.cfm?Index_Number=168103) (last visited Apr. 13, 2014).

showing H.P. Acthar Gel to be more effective than less expensive steroids used sub-optimal doses of steroids.<sup>245</sup> One hospital successfully treated eighteen of thirty babies with a high-dose oral steroid for two weeks, at a cost of \$200.<sup>246</sup> Only the twelve who did not respond were prescribed H.P. Acthar Gel, with five successfully treated.<sup>247</sup> The approach reportedly saved more than \$2 million.<sup>248</sup> The attending physician commented that the hospital has an obligation to monitor the cost to the healthcare system and make responsible decisions.<sup>249</sup>

Additionally, Questcor began marketing the drug for the other approved indications: multiple sclerosis, nephrotic syndrome, and rheumatologic conditions.<sup>250</sup> Since Acthar was approved for such use before the FDA required clinical trials to demonstrate efficacy—Acthar has grandfather status—there is similarly little evidence demonstrating cost effectiveness over cheaper alternatives for these uses.<sup>251</sup> As a result, Questcor did not have the expense or time commitment of clinical trials to demonstrate efficacy.<sup>252</sup> A spokesman for the company reportedly stated that the new price of H.P. Acthar Gel was set to make the company viable, based solely on sales for infantile spasms; executives assumed at the time that the high price would preclude other uses.<sup>253</sup> The company began to sponsor more studies with H.P. Acthar Gel, which was not possible until the drug became financially viable.<sup>254</sup> In addition to the new research, Questcor operates a free drug program, ensuring improved accessibility in contrast to when the product was cheaper but often in short supply.<sup>255</sup>

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<sup>245</sup> Pollack, *supra* note 233.

<sup>246</sup> *Id.*

<sup>247</sup> *Id.*

<sup>248</sup> *Id.*

<sup>249</sup> *Id.* A physician reported that a hospital at which he had privileges maintained a policy not to hospitalize a child with spasms without first seeking pre-authorization; in practice, however, no child was reportedly turned away due to financial reasons. *Id.*

<sup>250</sup> *Id.* A course of treatment for nephrotic syndrome can run \$250,000, while a shorter treatment for a multiple sclerosis relapse typically costs \$40,000. *Id.*

<sup>251</sup> *Id.*

<sup>252</sup> *Id.*

<sup>253</sup> *Id.*

<sup>254</sup> *Id.* “[A] study that . . . sought to determine whether multiple sclerosis patients who did not have a good response to steroids should be treated with either another round of steroids or with Acthar [was terminated] midway through “to analyze data,” according to the summary of the trial on the federal clinical trial database.” *Id.* It is hypothesized that a published “negative result could have jeopardized already growing sales for multiple sclerosis.” *Id.* The company responded that “the trial fell hopelessly behind its goal in recruiting patients.” *Id.* This highlights a new trend in clinical studies called adaptive trials. U.S. FOOD AND DRUG ADMIN., GUIDANCE FOR INDUSTRY: ADOPTIVE DESIGN CLINICAL TRIALS FOR DRUGS AND BIOLOGICS 1–2 (Proposed Official Draft Guidance 2010), available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM201790.pdf>.

<sup>255</sup> Pollack, *supra* note 233. Questcor has assistance programs for patients who cannot afford the drug; the company helps with insurance co-payments, to ensure that a patient’s inability to pay

However, while access programs stave off consumer protests, Questcor can simply shift the associated cost onto payers.<sup>256</sup>

According to the New York Times article, approximately “10 percent of the drug’s sales are for infantile spasms.”<sup>257</sup> The new uses represent significant opportunity for H.P. Acthar Gel and Questcor, and a representative indicated that Questcor does not intend to develop other products.<sup>258</sup> “Sales of Acthar, which account for essentially all of Questcor’s sales, totaled nearly \$350 million in the first nine months [of 2012], up 145 percent from the period a year earlier.”<sup>259</sup> “In the five years [following the H.P. Acthar Gel] price increase in August 2007, Questcor shares rose from around 60 cents to about \$50, in one of the best performances of any stock in any industry.”<sup>260</sup> A Questcor representative stated, “[w]e could lower the price and make less money . . . and then we would be sued by our shareholders.”<sup>261</sup> However, in September, the shares plummeted after Aetna indicated it would no longer pay for H.P. Acthar Gel, “except to treat infantile spasms, because of lack of evidence the drug worked for other diseases.”<sup>262</sup>

Yet, there may soon be competition in this space too. Novartis, which sells a synthetic version under the trade name Synacthen in Europe, has applied for a U.S. trademark.<sup>263</sup> Also, Cerium Pharmaceuticals recently received U.S. orphan-drug designation for Synacthen in the treatment of infantile spasms.<sup>264</sup> While it seems apparent that repurposing of drugs and biologics under the ODA has impacted the cost of medication, a larger threat to the affordability of prescription drugs potentially looms.

## VII. PHARMACOGENOMICS (PGX)

The ODA potentially has broader ramifications for healthcare costs when viewed through the prism of genomic science. An individual’s genome plays a significant role in disease susceptibility and drug

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does not inhibit use of the drug. *Id.* A staff of thirty—about one staff member for each of the roughly thirty prescriptions it gets in a typical day for all uses—is tasked with working on insurance reimbursements. *Id.* NORD also operated a patient assistance program with discounts up to 100%. Samson, *supra* note 72, at A15.

<sup>256</sup> Pollack, *supra* note 233.

<sup>257</sup> *Id.*

<sup>258</sup> *Id.*

<sup>259</sup> *Id.*

<sup>260</sup> *Id.*

<sup>261</sup> *Id.*

<sup>262</sup> *Id.*

<sup>263</sup> *Id.*

<sup>264</sup> *Id.*

response.<sup>265</sup> For example, at opposite ends of the spectrum, people potentially can be identified as poor metabolizers (“PMs”) or ultrarapid metabolizers (“UMs”) of specific drugs based on the known biochemical pathways.<sup>266</sup> Genetic tests or biomarkers can inform these classifications.<sup>267</sup> Pharmacogenomic data has already resulted in changes to FDA-approved labeling.<sup>268</sup> In applying standard pharmacology to genomics, pharmacogenomics (“PGx”) will be a substantial driver in the personalized medicine revolution.<sup>269</sup> PGx refers broadly to the study of drug exposure and/or response as related to variations in DNA and RNA characteristics.<sup>270</sup> “*Drug exposure* refers to the [pharmacokinetic (“PK”)] profile following administration.”<sup>271</sup> “*Drug response* refers to the [pharmacodynamics (“PD”)] response to the drug; that is, all of the effects of the drug on any physiologic and pathologic processes, including those related to effectiveness and those related to adverse reactions.”<sup>272</sup> According to the FDA, “[t]he promise of pharmacogenomics lies in its potential to help identify sources of inter-individual variability in drug response

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<sup>265</sup> Liewei Wang et al., *Genomics and Drug Response*, 364 NEW ENG. J. MED. 1144, 1144 (2011). While certainly, social determinants of disease also play a significant role, as do other environmental factors. *Genomics and Health*, CTRS. FOR DISEASE CONTROL & PREVENTION, <http://www.cdc.gov/genomics/public/> (last updated July 29, 2013).

<sup>266</sup> *Pharmacogenomics and its Role in Drug Safety*, 1 FDA DRUG SAFETY NEWSL. 12, 24 (2008), available at <http://www.fda.gov/downloads/Drugs/DrugSafety/DrugSafetyNewsletter/ucm109169.pdf>; see also Jai Shah, *Concept and Putative Application of Pharmacogenetics and Pharmacogenomics*, 12 HEALTH L. REV. 3, 5 (2004).

<sup>267</sup> See U.S. FOOD AND DRUG ADMIN., GUIDANCE FOR INDUSTRY: CLINICAL PHARMACOGENOMICS: PREMARKET EVALUATION IN EARLY-PHASE CLINICAL STUDIES AND RECOMMENDATIONS FOR LABELING 3 (2013), available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM337169.pdf> [hereinafter FDA CLINICAL PHARMACOGENOMICS].

It is [the] FDA’s position that if a *companion diagnostic* is required for therapeutic selection, an FDA-approved or -cleared test will be required at the same time that the drug is approved. An in vitro PGx test would be considered a companion diagnostic device if it will provide information that is essential for the safe and effective use of a therapeutic product as directed in labeling.

*Id.* at 7 (emphasis in original).

<sup>268</sup> Cetuximab/K-ras is such an example. *Table of Pharmacogenomic Biomarkers in Drug Labeling*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm> (last updated Jan. 22, 2014). The Warfarin and VKORC1 interaction is another prominent example. *Id.*

<sup>269</sup> Hong-Guang Xie & Felix W. Freuh, *Pharmacogenomics Steps Toward Personalized Medicine*, 2 PERSONALIZED MED. 325, 325 (2005).

<sup>270</sup> FDA CLINICAL PHARMACOGENOMICS, *supra* note 267; U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: E15 DEFINITIONS FOR GENOMIC BIOMARKERS, PHARMACOGENOMICS, PHARMACOGENETICS, GENOMIC DATA AND SAMPLE CODING CATEGORIES 3 (2008), available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073162.pdf>.

<sup>271</sup> FDA CLINICAL PHARMACOGENOMICS, *supra* note 267, at 4 (emphasis in original).

<sup>272</sup> *Id.* (emphasis in original).

(both effectiveness and toxicity); this information will make it possible to individualize therapy with the intent of maximizing effectiveness and minimizing risk.”<sup>273</sup> In this manner, the use of pharmacogenomics fulfills the intent of the ODA by incentivizing industry investment in diseases that impact a small number of patients.

Pharmacogenomics will likely have significant implications for clinical trials.<sup>274</sup> The potential for parallel trials targeting various subgroups could increase business costs related to FDA approval.<sup>275</sup> Also, it has been suggested that manipulation of safety and efficacy data based on preferential selection of research participants into particular cohorts with advantageous genetic markers could skew results, particularly since submission of pharmacogenomic data is not required by the FDA.<sup>276</sup> If so, demonstrations of clinical superiority, which do not require a new chemical entity, could become highly susceptible to the inclusion and exclusion of particular research participants from the test and control groups.<sup>277</sup> Consequently, Loughnot suggests that clinical superiority should be demonstrated using cohorts of research participants with similar genetic profiles to avoid manipulation of trial results and unwarranted extension of ODA incentives.<sup>278</sup>

Moreover, pharmacogenomics implicates the ODA by enabling a sponsor to request orphan-drug designation for use of that drug in a subset of persons with a disease or condition that may not otherwise be rare. The manner in which FDA’s purpose has been to establish safety and efficacy on a population scale, PGx promises to ensure safety and efficacy on the individual level.<sup>279</sup> Medical science will be able to

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<sup>273</sup> U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: PHARMACOGENOMIC DATA SUBMISSIONS 2 (2005), available at <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm126957.pdf>.

<sup>274</sup> See generally Loughnot, *supra* note 142, at 375–76.

<sup>275</sup> Jai Shah, *Economic and Regulatory Considerations in Pharmacogenomics for Drug Licensing and Healthcare*, 21 NATURE BIOTECHNOLOGY 747, 749 (2003) (noting the possible conundrum created by the identification of drugs with major benefit to few and marginal benefit to many and the extent to which payers will cover such treatments in light of cost-effectiveness analyses).

<sup>276</sup> Loughnot, *supra* note 142, at 366–67; FDA PHARMACOGENOMIC DATA SUBMISSIONS, *supra* note 273, at 5.

<sup>277</sup> Loughnot, *supra* note 142, at 366–67.

<sup>278</sup> *Id.* at 379.

<sup>279</sup> See generally FDA PHARMACOGENOMIC DATA SUBMISSIONS, *supra* note 273 at 3; Michael M. Hopkins et al., *Putting pharmacogenetics into practice*, 24 NATURE BIOTECHNOLOGY 403, 406 (2006), <http://www.nature.com/nbt/journal/v24/n4/pdf/nbt0406-403.pdf>. The general challenges to the FDA’s regulatory process will likely require significant adaptation. Submission of PGx data is currently encouraged, although voluntary. FDA PHARMACOGENOMIC DATA SUBMISSIONS, *supra* note 273, at 4. Increased costs incidental to verification in increasingly diverse sub-classifications of research participants may weigh in favor of post-market efficacy surveillance, as balanced against the ethical considerations of distributive justice in demonstrating safety in all possible classes. See generally Deepak Gupta, *Pharmacogenomics in Drug Discovery and Development*, 2 J. OF DEVELOPING DRUGS

identify disease subsets using biomarkers. Since the pathogenesis of disease is often multi-factorial, the same disorder could be subdivided into classifications based on unique genetic signatures, such as single nucleotide polymorphisms (“SNPs”).<sup>280</sup> Illustratively, a subpopulation of patients with various forms of cancer expresses the HER2 oncogene, which the monoclonal antibody, trastuzumab, was designed to inhibit.<sup>281</sup> In this manner, pharmacogenomics shares many similarities with orphan products.<sup>282</sup> Pharmacogenomics has been instrumental in the growth of orphan drug designations, and, like orphan drugs, is being used most widely in connection with cancer therapeutics.<sup>283</sup> Two brief case studies follow.

#### A. Case Study: Kalydeco® and Vertex Pharmaceuticals

In the U.S., approximately 30,000 people have cystic fibrosis, caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene that transports chloride ions across cell membranes.<sup>284</sup> Those afflicted have a propensity to collect mucus in the lungs, resulting in infections and lung damage.<sup>285</sup> The average life expectancy is 37 years.<sup>286</sup> Kalydeco (ivacaftor), developed by Vertex Pharmaceuticals, targets a specific mutation (G551D) in the gene that accounts for 4%—or approximately 1,200—of cystic fibrosis cases in the U.S.<sup>287</sup> Kalydeco received orphan-drug designation on December 20,

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1, 1–2 (2013), <http://www.omicsgroup.org/journals/pharmacogenomics-in-drug-discovery-and-development-2329-6631.1000e126.pdf>.

<sup>280</sup> Alain Vignal et al., *A Review on SNP and Other Types of Molecular Markers and Their Use in Animal Genetics*, 275 GENETICS SELECTION EVOLUTION 275, 278 (2002), available at <http://www.biomedcentral.com/content/pdf/1297-9686-34-3-275.pdf>. A SNP is a DNA sequence variation occurring when a single nucleotide—A, T, C or G—in the genome differs between paired human chromosomes. *Id.* at 277–78. “[T]he spontaneous mutation rate . . . occurs at each genetic locus with a frequency of approximately 1 per 100,000 per generation.” Jess G. Thoene, *Curing the Orphan Drug Act*, 251 SCI. 1158, 1158 (1991).

<sup>281</sup> Shah, *supra* note 275, at 747; see also *Search Orphan Drug Designations and Approvals*, U.S. FOOD & DRUG ADMIN., [http://www.accessdata.fda.gov/scripts/opdlisting/ood/OOPD\\_Results\\_2.cfm?Index\\_Number=129399](http://www.accessdata.fda.gov/scripts/opdlisting/ood/OOPD_Results_2.cfm?Index_Number=129399) (last visited Apr. 13, 2014) (stating that Herceptin is known generically as trastuzumab).

<sup>282</sup> Shah, *supra* note 275, at 749; see also Wouter Boon & Ellen Moors, *Exploring Emerging Technologies Using Metaphor—A Study of Orphan Drugs and Pharmacogenomics*, 66 SOC. SCI. & MED. 1915 (2008).

<sup>283</sup> Loughnot, *supra* note 142, at 366–67, 380.

<sup>284</sup> Andrew Pollack, *FDA Approves New Cystic Fibrosis Drug*, N.Y. TIMES, Jan. 31, 2012, at G551D, available at [http://www.nytimes.com/2012/02/01/business/fda-approves-cystic-fibrosis-drug.html?\\_r=0](http://www.nytimes.com/2012/02/01/business/fda-approves-cystic-fibrosis-drug.html?_r=0).

<sup>285</sup> *Id.*

<sup>286</sup> *Id.*

<sup>287</sup> *Id.*

2006 and market approval and exclusivity on January 31, 2012.<sup>288</sup> The relevant patents will run through approximately 2026,<sup>289</sup> well beyond the exclusivity period which expires in 2019. The duration of the FDA approval process exceeded expectation, coming nearly three months prior to the target deadline.<sup>290</sup> “The FDA . . . based its approval on two placebo-controlled studies involving a combined 213 patients [over 48 weeks].”<sup>291</sup> Kalydeco will cost an estimated \$294,000 a year.<sup>292</sup>

Vertex received \$75 million from the Cystic Fibrosis Foundation, “an example of how patient advocacy groups have been taking a more direct role in drug development”—particularly in the orphan space—in what has been referred to as “venture philanthropy.”<sup>293</sup> The president of the foundation explained that the contribution to Vertex was intended to establish a working relationship and to lower the risk associated with development of products for rare diseases.<sup>294</sup> The pharmaceutical company was also able to avail itself of the foundation’s patient registry and established network of care centers, facilitating participant enrollment in clinical trials.<sup>295</sup> In return, Vertex agreed to pay royalties to the foundation, money from sales of the drug that reportedly will be reinvested in additional research.<sup>296</sup>

### *B. Case Study: Xalkori® and Pfizer*

Xalkori (crizotinib), a tyrosine kinase inhibitor that blocks the anaplastic lymphoma kinase (“ALK”) enzymes that can stimulate cancer growth, is an oral drug indicated for the treatment of approximately five percent of those with non-small cell lung cancer (“NSCLC”).<sup>297</sup> An estimated 45,000 patients worldwide are diagnosed with metastatic ALK-positive NSCLC every year.<sup>298</sup> The drug is developed and manufactured by Pfizer, and the corresponding patents

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<sup>288</sup> *Search Orphan Drug Designations and Approvals*, U.S. FOOD & DRUG ADMIN., [http://www.accessdata.fda.gov/scripts/opdlisting/oopd/OOPD\\_Results\\_2.cfm?Index\\_Number=228306](http://www.accessdata.fda.gov/scripts/opdlisting/oopd/OOPD_Results_2.cfm?Index_Number=228306) (last visited Apr. 13, 2014).

<sup>289</sup> *See Generic Kalydeco Availability*, DRUGS.COM, <http://www.drugs.com/availability/generic-kalydeco.html> (last visited Apr. 24, 2014) [hereinafter *Generic Kalydeco Availability*]; *see also* U.S. Patent No. 8,410,274 (filed Jan. 26, 2012).

<sup>290</sup> Pollack, *supra* note 284.

<sup>291</sup> *Id.*; *see also* Barrett et al., *supra* note 175, at R5.

<sup>292</sup> Pollack, *supra* note 284.

<sup>293</sup> *Id.*

<sup>294</sup> *Id.*

<sup>295</sup> *See Care Center Network*, CYSTIC FIBROSIS FOUND., <http://www.cff.org/LivingWithCF/CareCenterNetwork/> (last visited Mar. 9, 2014).

<sup>296</sup> Pollack, *supra* note 284.

<sup>297</sup> *Xalkori—Treatment for Non-Small Cell Lung Cancer*, DRUGDEVELOPMENT-TECHNOLOGY.COM, <http://www.drugdevelopment-technology.com/projects/xalkori---treatment-for-nonsmall-cell-lung-cancer/> (last visited Mar. 9, 2014) [hereinafter *Xalkori*].

<sup>298</sup> *Id.*



will run through approximately 2025.<sup>299</sup> Xalkori obtained orphan drug designation for this indication in September 2010,<sup>300</sup> and received fast track designation in December 2010.<sup>301</sup> Pfizer filed a NDA in March 2011, and the FDA approved the drug for the treatment of ALK-positive NSCLC on August 26, 2011.<sup>302</sup> The approval was based on data from 255 patients enrolled in two then-ongoing clinical trials that had begun in January 2010.<sup>303</sup> Xalkori received FDA approval in less than five months—only four years from identification of the target—and “represent[s] the first time that a targeted cancer therapeutic was approved . . . based on Phase I data.”<sup>304</sup> Clinical trials showed a median gain of 5.1 months in progression-free survival compared with standard therapy.<sup>305</sup> The researchers initially spent six years investigating the molecule’s interaction with another gene in gastric tumors but were redirected by a publication in *Nature* describing the role of the ALK fusion gene in NSCLC, resulting in a shift in the gene target and the patient population.<sup>306</sup> Pfizer’s president of worldwide R&D touted the “remaining commercial potential in inhibiting the ALK translocation, with several additional indications currently in Phase I trials, and Pfizer’s ongoing exploration of Xalkori’s other targets.”<sup>307</sup>

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<sup>299</sup> See *Generic Xalkori Availability*, DRUGS.COM, <http://www.drugs.com/availability/generic-xalkori.html> (last visited Apr. 13, 2014) [hereinafter *Generic Xalkori Availability*]; see also U.S. Patent No. 7,825,137 (filed Nov. 23, 2006).

<sup>300</sup> See *Search Orphan Drug Designations and Approvals*, U.S. FOOD & DRUG ADMIN., [http://www.accessdata.fda.gov/scripts/opdlisting/oopd/OOPD\\_Results\\_2.cfm?Index\\_Number=310610](http://www.accessdata.fda.gov/scripts/opdlisting/oopd/OOPD_Results_2.cfm?Index_Number=310610) (last visited Mar. 9, 2014). Crizotinib has two additional orphan designations from 2012, for treatment of anaplastic large cell lymphoma and neuroblastoma. See *Search Orphan Drug Designations and Approvals*, U.S. FOOD & DRUG ADMIN., [http://www.accessdata.fda.gov/scripts/opdlisting/oopd/OOPD\\_Results\\_2.cfm?Index\\_Number=379712](http://www.accessdata.fda.gov/scripts/opdlisting/oopd/OOPD_Results_2.cfm?Index_Number=379712) (last visited Mar. 9, 2014); *Search Orphan Drug Designations and Approvals*, U.S. FOOD & DRUG ADMIN., [http://www.accessdata.fda.gov/scripts/opdlisting/oopd/OOPD\\_Results\\_2.cfm?Index\\_Number=379812](http://www.accessdata.fda.gov/scripts/opdlisting/oopd/OOPD_Results_2.cfm?Index_Number=379812) (last visited Apr. 13, 2014).

<sup>301</sup> *Xalkori*, *supra* note 297.

<sup>302</sup> U.S. FOOD & DRUG ADMIN., CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICALS REVIEW(S) 1 (2011), available at [http://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2011/202570Orig1s000ClinPharmR.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/202570Orig1s000ClinPharmR.pdf); U.S. FOOD & DRUG ADMIN., 2011 NOVEL NEW DRUGS 14 (2012), available at <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DrugInnovation/ucm293663.pdf>. Xalkori also received marketing exclusivity as a new chemical entity, which runs through 2016. *Generic Xalkori Availability*, *supra* note 299.

<sup>303</sup> *Xalkori*, *supra* note 297. Objective response rates (ORR) between 50 and 60% were observed. *Id.*

<sup>304</sup> Chris Morrison, *Pfizer’s Dolsten Sees a Bright Future for Xalkoi and Pfizer Oncology*, THE IN VIVO BLOG (Feb. 15, 2012, 4:22 P.M.), <http://invivoblog.blogspot.com/2012/02/pfizers-dolsten-sees-bright-future-for.html>.

<sup>305</sup> Selina McKee, *Final NICE ‘No’ for Pfizer’s Xalkori*, PHARMATIMES (Sept. 25, 2013), [http://www.pharmatimes.com/article/13-09-25/Final\\_NICE\\_no\\_for\\_Pfizer\\_s\\_Xalkori.aspx](http://www.pharmatimes.com/article/13-09-25/Final_NICE_no_for_Pfizer_s_Xalkori.aspx).

<sup>306</sup> Morrison, *supra* note 304.

<sup>307</sup> *Id.* (including c-MET and recently disclosed ROS1).

In the U.S., a regimen of the Xalkori—two pills daily—costs approximately \$80,000.<sup>308</sup> The pathology service to determine individual applicability costs approximately \$1,500, including \$250 for the biomarker test itself.<sup>309</sup> Most managed care organizations reimburse for Xalkori.<sup>310</sup> “[T]hree-quarters of surveyed U.S. oncologists prescribe Pfizer’s Xalkori for the treatment of [NSCLC] just 10 months after the drug’s launch, illustrating the power of a targeted agent with a strongly predictive biomarker to achieve usage, despite a small eligible patient population.”<sup>311</sup>

After submitting a marketing authorization application for Xalkori to the European Medicines Agency (EMA) in August 2011, Pfizer received conditional approval from the European Commission (EC) for the treatment of advanced NSCLC in October 2012.<sup>312</sup> However, despite EMA approval and recognition of clinical effectiveness, the UK’s National Institute for Health and Care Excellence (NICE) has determined that the drug is not cost effective as compared to existing therapies and has declined to cover the drug as part of the National Health Service.<sup>313</sup> Pfizer responded: “the UK’s limited and slow-paced adoption of innovative medicines such as crizotinib poses a real threat to both the government’s goal to have UK cancer outcomes among the highest in Europe and its vision to make the UK a world leader in life sciences.”<sup>314</sup>

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<sup>308</sup> Matthew Herper, *Gene Test For Pfizer Cancer Drug to Cost \$1,500 Per Patient*, FORBES (Aug. 29, 2011, 12:29 P.M.), <http://www.forbes.com/sites/matthewherper/2011/08/29/gene-test-for-pfizer-cancer-drug-to-cost-1500-per-patient/>; see also J. Leonard Lichtenfeld, *Crizotinib Approval For Lung Cancer Shows Our Miracles Aren’t Getting Less Expensive*, DR. LEN’S CANCER BLOG (Aug. 30, 2011), <http://www.cancer.org/aboutus/drlensblog/post/2011/08/30/crizotinib-approval-for-lung-cancer-shows-our-miracles-arent-getting-less-expensive.aspx> (showing crizotinib (Xalkori®) costs \$115,200 per year).

<sup>309</sup> Herper, *supra* note 308. The expense of the test is weighed against the cost-savings of increased efficacy, reduced sequela, and increased adherence. Shah, *supra* note 275, at 749. Of note, an author describes the potential cost of defensive medicine, with the impulse to order a myriad of genetic tests prior to treatment in order to avoid malpractice liability. *Id.* at 751. Another foreseeable difficulty involves the recalibration of the risk/benefit analysis in the circumstance of last resort treatments. *Id.*

<sup>310</sup> *For the Treatment of Non-Small-Cell Lung Cancer (NSCLC), Three-Quarters of Surveyed U.S. Oncologists Prescribe Pfizer’s Xalkori Just 10 Months After the Drug’s Launch*, DECISION RES. (June 19, 2012), <http://decisionresources.com/News-and-Events/Press-Releases/Breast-Cancer-Non-Small-Cell-Lung-Cancer-061912>.

<sup>311</sup> *Id.*

<sup>312</sup> *Xalkori*, *supra* note 297.

<sup>313</sup> NAT’L INST. FOR HEALTH AND CLINICAL EXCELLENCE, CRIZOTINIB FOR PREVIOUSLY TREATED NON-SMALL-CELL LUNG CANCER ASSOCIATED WITH AN ANAPLASTIC LYMPHOMA KINASE FUSION GENE, 38 (Sept. 2013), available at <http://www.nice.org.uk/nicemedia/live/14282/65275/65275.pdf>. NICE concluded that the cost per Quality-Adjusted Life Year (QALY) for Xalkori compared with docetaxel would be more than £100,000 per QALY gained, and compared with best supportive care more than £50,200 per QALY gained, and so far and beyond what is normally considered a cost effective use of NHS resources. *Id.* at 34.

<sup>314</sup> McKee, *supra* note 305.

### VIII. PROPOSED AMENDMENTS TO THE ORPHAN DRUG ACT

Legislative amendments have been proposed to cure the perceived ills of the ODA, employing both prospective and retrospective approaches. As a retrospective tactic, an amendment proposed in 1992 would have made continued exclusivity conditional upon maintaining total profits below a \$200 million threshold after a two year period.<sup>315</sup> Exceeding the threshold, inclusive of revenue generated from off-label uses, would have resulted in loss of exclusivity.<sup>316</sup> Other amendments proposed different triggers, including the termination of marketing exclusivity once the rare disease population exceeded 200,000 individuals.<sup>317</sup> Loughnot has criticized this proposal because sponsors potentially would be disincentivized to develop treatments for conditions affecting close to 200,000 people, for fear of prematurely losing exclusivity.<sup>318</sup> Still other proposed amendments have relied upon the particularized cost of developing the drug as the benchmark for calculating tax owed—all related profits exceeding the threshold taxed significantly so as to prevent the perceived windfall.<sup>319</sup> The same author challenged the wisdom of these approaches, as administratively unwieldy and anathema to the secrecy maintained by the pharmaceutical industry with regard to costs and profits.<sup>320</sup> Additionally, Loughnot noted that the actual cost of any given drug often incorporates estimated development expenses associated with failed drugs.<sup>321</sup> Finally, he lamented that a windfall tax would only result in pass-through costs paid by patients and payors.<sup>322</sup>

Instead of *post-hoc* adjustments in the Act's scheme, preventative measures have also been proposed. In November 1990, both houses of Congress passed an amendment which would have required analysis of the level of industry interest in development of the putative orphan drug to encourage competition where present—yet discouraging a “me too” approach; the bill was vetoed by then-President Bush.<sup>323</sup> Of note,

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<sup>315</sup> Pulsinelli, *supra* note 31 at 332.

<sup>316</sup> *Id.*

<sup>317</sup> *Id.* at 323 (noting this would have affected AIDS treatments, such as AZT, for which the affected population grew well past 200,000 after FDA already had conferred orphan designation).

<sup>318</sup> Loughnot, *supra* note 143 at 378. Though, one might argue such a scheme would—in this burgeoning era of shared responsibility in healthcare—provide the greatest incentive to create extremely effective treatments and active investment in their continued success.

<sup>319</sup> Pulsinelli, *supra* note 31, at 336.

<sup>320</sup> Loughnot, *supra* note 143, at 378.

<sup>321</sup> *Id.*

<sup>322</sup> *Id.*

<sup>323</sup> Orphan Drug Amendments of 1990, H.R. 4638, 101st Cong. (1990).

As proposed, such an amendment would have permitted simultaneous licensing of the same orphan product for the same indication if (i) the second company requests orphan designation within 6 months of publication by the FDA of its action to designate the drug for the first company; (ii) the second company

Wellman-Labadie and Zhou found a correlation between a slowdown in orphan approvals and the proposed amendments of the early 1990s, suggesting the sensitivity of the market to the uncertainty associated with legislation aiming to curtail incentives.<sup>324</sup> It is clear that the drafters of any changes to the incentive structure of the ODA must be judicious so as not to stifle progress in the development of these products, as rare disease remains an area with significant unmet need.

### IX. CONCLUSION: THE NEW ORPHANS?

Numerous policy proposals have been proffered to curtail the perceived abuses and extravagancies of the ODA, as it has been applied to and exploited in industry. As noted above, suggestions have included shortening the exclusivity period, allowing for limited competition during the exclusivity period, implementing a cap on drug prices, and levying a tax on manufacturer profits.<sup>325</sup> In an effort to increase application scrutiny, Loughnot identified the ODA's nebulous definition of clinically superior as possible vehicle for systematically circumscribing the ODA's incentives.<sup>326</sup> It has also been suggested the FDA confer market exclusivity on a case-by-case basis, considering such factors as the extent to which the company's investment ought to be rewarded, the degree to which the application for marketing approval relies on government research, and the degree to which the drug responds to an unmet or important public health need.<sup>327</sup> Surely, the lack of certainty in any amorphous standard or retroactive approach would quickly draw the ire of industry, stymie venture capital investment on the front end, and further delay a process which is already complex and protracted.

The cost of orphan products remains controversial and symptomatic of the wider inflationary trend of healthcare costs. Based on the case studies detailed above, it is reasonable to inquire as to true

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initiates human clinical trials not more than 12 months after the first company initiated clinical trials; and (iii) the second company submits an approvable new drug application to the FDA no more than 1 year after the first company submits its new drug application.

Toene, *supra* note 280, at 1159; David Duffield Rohde, *The Orphan Drug Act: An Engine of Innovation? At What Cost?*, 55 FOOD & DRUG L.J. 125, 137 (2000).

<sup>324</sup> Wellman-Labadie & Zhou, *supra* note 50, at 220 (noting a second slowdown in orphan product approvals during the 2000 recession that stifled start-up capital).

<sup>325</sup> Greenwood, *supra* note 47, at 11–13.

<sup>326</sup> Loughnot, *supra* note 142, at 366.

<sup>327</sup> See generally Greenwood, *supra* note 47 at 1–14 (assessing the merits of calibrated incentives); Wills Hughes-Wilson et al., *Paying for the Orphan Drug System: Break or Bend? Is it Time for a New Evaluation System for Payers in Europe to Take Account of New Rare Disease Treatments*, 7 ORPHANET J. RARE DISEASES 1, 5 (2012), available at <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3582462/>.

significance and impact of market exclusivity for orphan products. True monopoly power deriving from the ODA is likely only created in a small percentage of cases. Through market exclusivity, the ODA alone bars competition—to the extent that it would otherwise exist due to the small market—only for those drugs that are off-patent and generally repurposed.<sup>328</sup> Barring expensive litigation, Kalydeco and Xalcori will remain under patent after market exclusivity expires.<sup>329</sup> Seoane-Vazquez found a positive but modest overall impact of exclusivity on monopoly power for new molecular entities under patent.<sup>330</sup>

Even in the case of H.P. Acthar Gel, Questcor was able to raise price owing to the unmet need, prior to and in anticipation of receiving market exclusivity.<sup>331</sup> Market exclusivity certainly provides an added barrier to entry for would-be competitors but, even then, only where there are no other FDA-approved indications.<sup>332</sup> Despite the rarity of repeat preterm labor, a generic manufacturer hopes to enter the market and will compete—assuming an advantageous price point—with Makena through off-label prescriptions.<sup>333</sup> H.P. Acthar Gel, too, appears likely to face competition based on the potential for a follow-on company to market unprotected, yet nonetheless FDA-approved, indications. Furthermore, the more new uses discovered, the larger the market and the greater the likelihood that competitors will be drawn to the space—such new indications not necessarily protected by exclusivity.<sup>334</sup> Though both case studies involving repurposed molecules do demonstrate the possibility of competition in small

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<sup>328</sup> Randall Morin et al., *Adopt IP Protections to Ensure Regulatory Exclusivity for Orphan Drugs*, 31 ASSOC. OF CORPPRTE COUNSEL 79, 83 (Sept. 2013), available at [http://www.choate.com/uploads/1178/doc/ACC\\_Docket\\_-\\_Adopt\\_IP\\_Protections\\_to\\_Ensure\\_Regulatory\\_Exclusivity\\_for\\_Orphan\\_Drugs.pdf](http://www.choate.com/uploads/1178/doc/ACC_Docket_-_Adopt_IP_Protections_to_Ensure_Regulatory_Exclusivity_for_Orphan_Drugs.pdf). This statement excludes those drugs that never received FDA approval for their original purpose prior to patent expiration, conceivably allowing for market exclusivity once FDA approval is received for that original purpose—without being repurposed. *Id.* Also, it will be interesting to monitor whether the pharmaceutical industry will make a concerted push to obtain orphan designation for new indications of drugs that have recently or will soon go off patent, in an attempt to extend monopoly pricing.

<sup>329</sup> *Generic Xalkori Availability*, *supra* note 299; *Generic Kalydeco Availability*, *supra* note 289.

<sup>330</sup> Seoane-Vazquez et al., *supra* note 44 (showing that “only 1 in 10 NME Orphan drugs benefited directly from the ODA exclusivity” and monopoly power is extended by only 0.8 years on average beyond patent expiration).

<sup>331</sup> Pollack, *supra* note 233. The ability to raise price without market exclusivity might also have been enabled by the complexity of manufacturing such a biologic and any trade secrets involved in that process.

<sup>332</sup> It would not seem prudent or inspire investor confidence for biotech firms to forego patent protection in sole reliance on FDA exclusivity, to avoid the costs associated with patents.

<sup>333</sup> See *Current Progress Towards ANDA Approval of Hydroxyprogesterone Caproate Injection*, USP, MCGUFF PHARMS. INC. (June 13, 2013, 5:01 P.M.), <http://www.mcguffpharmaceuticals.com/About/hydroxyprogesterone-caproate-injection.aspx>.

<sup>334</sup> If the original manufacturer receives exclusivity for the new indication or clinically superior form of the product, there will be no price competition until a competitor is able to and enters the market for the original indication.

markets, it is not clear that competition created by market forces alone would sufficiently contain prices.

Off-patent, repurposed molecules will generally always have an indication of which a manufacturer may take advantage to compete indirectly with an orphan product at some point in that branded product's exclusivity period. With the increasing impact of evidence-based medicine and cost-effectiveness research at both the prescriber and payor levels, there is reason to hope that the most efficient treatments will be utilized. Increasingly, healthcare providers will have both vested financial interests in clinical efficiency and access to health outcomes data that will continue to augment simple reliance on FDA approvals for specific indications, since the FDA has no authority to control prescribing practices of FDA-approved drugs. In fact, a recent study investigated four orphan drugs and found that nearly \$500 million of revenue was generated from off-label sales.<sup>335</sup> While not to suggest that all money spent on off-label drugs resulted from favorable competition and resulted in clinical efficiencies,<sup>336</sup> the market is not insignificant.

Nonetheless, as the two case studies involving pharmacogenomics exemplify, industry has successfully pursued treatments for rare disease, but the ODA is not responsible for the exorbitant expense of new orphan drugs. Rather, the small market size and, often, longer patent terms drive pricing. Small markets both demand higher prices and inherently resist competition, the latter keeping prices elevated. Concurrent market exclusivity provides qualitative protection over patent rights but often does not itself enable monopoly pricing for new drugs. Thus, any alteration of the length of the market exclusivity would not seem to have a dramatic impact on orphan-product pricing.

The apparent dilemma specifically concerning the application of the ODA and resultant cost of drugs and biologics involves repurposed molecules. Of note, pharmacogenomics does not entirely negate the issue of repositioning. While it might seem inherent in the notion of personalized medicine that therapies will not be as amenable to repurposing—obviating need for reform looking forward—many gene-specific drugs are, in fact, not individual or even disease specific—particularly in cancer therapeutics—allowing for the possibility of repositioning and monopoly pricing after patent expiration.<sup>337</sup> Additionally, it has been observed that while “[d]rugs designed to address a specific genetic deficit or replace a missing enzyme or protein, including all of the enzyme replacement therapies . . . have

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<sup>335</sup> Kesselheim et al., *supra* note 216, at 6.

<sup>336</sup> In fact, the case study involving H.P. Acthar Gel indicates that much of the prescriptions were not based on persuasive scientific evidence.

<sup>337</sup> This obviously does not consider the possibility of new-use patents. Kirk Teska, *What Are Improvement Patents and New Use Patents?*, NOLO (2014), <http://www.nolo.com/legal-encyclopedia/improvement-patents-new-use-patents-30250.html>.

little potential for true repurposing . . . [they] may be repositioned to embrace variants of the original disease as they are identified.”<sup>338</sup> Furthermore, pharmacogenomics can be utilized to reevaluate failed drug candidates through review and genetic profiling of research participants.<sup>339</sup>

Clearly consistent with the current framework of rewarding invention, the novel repositioning of a known drug, to treat rare disease or otherwise, warrants meaningful incentives and protections to spur such investment. Problematically, however, as demonstrated in the two case studies involving repurposed molecules, the uses were previously known and had become standard of care.<sup>340</sup> In both instances, the price increases dramatically upset market expectation, and to what end? Under such circumstances, the ODA primarily incentivizes FDA oversight, rather than development of and access to orphan products. Yet, again, the FDA traditionally is not concerned with cost or cost-effectiveness.<sup>341</sup> In performing a cost-benefit analysis of the ODA’s incentives, it is important to understand what value FDA oversight confers. FDA approval confirms safety and efficacy to the level required by governing regulations, demands compliance with good manufacturing practices (“GMPs”), necessitates pharmacovigilance, and potentially increases access through permissible marketing. Yet, was the ODA implemented to funnel existing treatments—though off-label—through the regulatory process? Also, is the value created by such oversight, as applied to repurposed molecules for which the use is already widespread, commensurate with the incentives provided for by the ODA, including seven years of market exclusivity? At least one author has concluded

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<sup>338</sup> Mathie, *supra* note 188.

<sup>339</sup> Shah, *supra* note 275, at 749–50.

<sup>340</sup> Sheldon Bradshaw, former chief counsel of the FDA, decried the FDA’s decision not to enforce KV’s market exclusivity, as against compounding pharmacies. Sheldon T. Bradshaw et al., *Did FDA Apply a Remedy Worse than the Disease in Refusing to Clear the Market of Unapproved Versions of Makena?*, 1 FDLI’S FOOD & DRUG POLICY FORUM 1, 4 (2011), available at <http://www.fdpi.org/docs/default-document-library/fdpi-policy-forum-11.pdf?sfvrsn=0>. In so doing, the authors equate the exercise of enforcement discretion with undermining the FDA’s mission, going so far as to rhetorically suggest that cheap drugs could be best obtained through abolition of the FDA. *Id.* Yet, the article fails to draw an important distinction between less expensive Makena and the two other examples cited, Elaprase and Cerezyme. *Id.* The relative price of the drugs should not be a determinative concern. Significantly, neither of the analogized drugs was previously available in the market. Mr. Bradshaw also worried that such discretion would effectively chill investment in the orphan space. *Id.* While difficult to quantify the degree of possible opportunity loss, use of the ODA has continued to increase in prevalence; tending to debunk this concern. While it is true that FDA should enforce exclusivity as against pharmacies that either compound a previously unavailable drug or mass produce a product, there should not be retroactive enforcement against as-needed compounding in the absence of demonstrated safety and efficacy problems.

<sup>341</sup> Greenwood, *supra* note 47, at 1–2, 13–14. Greenwood notes that the FDA has twice explicitly declined to consider cost in application of the ODA. *Id.* Both instances involved the statutory provisions for withdrawing market exclusivity: once in the context of defining clinical superiority and, again, in assessing sufficient quantities to meet public health need. *Id.* at 1 n.2.

that an appropriate equilibrium has not been reached in this circumstance.<sup>342</sup>

Consequently, practicable limiting criteria must then be explored to guard against price increases resulting from market exclusivity conferred to repurposed products under the ODA regimen. A novelty threshold or a standard-of-care test could be implemented before conferring orphan designation or market exclusivity. However, one of the important distinctions between regulatory exclusivities and patents is the absence of an absolute novelty requirement for the former. The intent of the ODA is not necessarily to bring *new* treatments to those afflicted with rare disease but more generally to “provide treatment for *presently untreated patients*.”<sup>343</sup> A standard of care test would place the FDA in the unenviable position of having to render such a determination.

Also, there has been recent controversy regarding the extent to which approval of a drug that has received orphan designation, and the incentives attendant thereto, should be severable from receipt of market exclusivity.<sup>344</sup> As noted above, the FDA’s final rule draws a definitive distinction between the requirements for orphan designation and for ultimate market exclusivity, in the context of clinical superiority. In fact, the FDA, in one instance, denied and, in another, withdrew market exclusivity for a biologic and a drug, respectively. The orphan drug received market approval, but the FDA did not confer exclusivity for failure to demonstrate clinical superiority over a previously approved drug, which had not been designated as an orphan drug and had not received market exclusivity therefor.<sup>345</sup> In response to a citizen petition, the FDA withdrew the biologic’s market exclusivity, concluding the Agency had erroneously informed the sponsor that clinical superiority had been demonstrated.<sup>346</sup> Therefore, there is precedent—albeit in a different context—to sever market approval for an orphan-designated product and market exclusivity. The FDA should have the necessary flexibility so market exclusivity need not automatically flow from orphan designation and subsequent approval in other exceptional circumstances. Many have encouraged

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<sup>342</sup> Greenwood, *supra* note 47, at 2.

<sup>343</sup> Orphan Drug Regulations, *supra* note 67, at 35,122 (emphasis in original) (citing *Genentech, Inc. v. Bowen*, 676 F. Supp. 301, 312 (D.D.C. 1987)).

<sup>344</sup> 21 C.F.R. § 316.3(b)(12) (2013) (“A designated drug will receive orphan-drug exclusive approval only if the same drug has not already been approved for the same use or indication.”).

<sup>345</sup> See Kurt R. Karst, *Another Orphan Drug Battle; Depomed Sues FDA Over GRALISE Orphan Drug Exclusivity*, FDA L. BLOG (Sept. 26, 2012 10:27 P.M.), [http://www.fdalawblog.net/fda\\_law\\_blog\\_hyman\\_phelps/2012/09/another-orphan-drug-battle-depomed-sues-fda-over-gralise-orphan-drug-exclusivity-.html](http://www.fdalawblog.net/fda_law_blog_hyman_phelps/2012/09/another-orphan-drug-battle-depomed-sues-fda-over-gralise-orphan-drug-exclusivity-.html).

<sup>346</sup> See Kurt R. Karst, *FDA Rescinds Orphan Drug Exclusivity for Wilate; A First-of-its-Kind Decision*, FDA L. BLOG (Aug. 8, 2012, 8:40 P.M.), [http://www.fdalawblog.net/fda\\_law\\_blog\\_hyman\\_phelps/2012/08/fda-rescinds-orphan-drug-exclusivity-for-wilate-a-first-of-its-kind-decision.html](http://www.fdalawblog.net/fda_law_blog_hyman_phelps/2012/08/fda-rescinds-orphan-drug-exclusivity-for-wilate-a-first-of-its-kind-decision.html).



and praised the flexibility exercised by the FDA in reviewing clinical trials associated with orphan products due to the unique challenges and unmet need surrounding rare disease—inuring to the benefit of industry and patients alike.<sup>347</sup> This flexibility ought to extend to administration of orphan incentives as well, likewise owing to the unique circumstances surrounding the small patient populations. Yet, such a paradigm would regrettably also add uncertainty to the market and complicate and lengthen the regulatory process.

As a system of imposed caps is likely an untenable solution, greater pricing transparency should be considered in the orphan space, or over the pharmaceutical market generally.<sup>348</sup> Profit margins should be defined across entire product portfolios, including all approved indications, not based on a single product or indication alone. Transparency will also have the virtue of enabling an assessment of whether the other ODA incentives that reduce development expenditures on the front end actually lessen the price of the drug to patients and payers. Similar to the amendments already proposed, pricing transparency could also enable the orphan program to mandate that a company identify an acceptable profit margin, with either a reduction in the cost of the drug thereafter or, alternatively, repayment of quantifiable government investments. Though less widely applicable, prescriptions or sales could be tracked as a measure of rarity, rather than a purely monetary-based threshold. Again, the gross profit—freely established by the company—would be maintained, with a price reduction per dose once the use of the drug exceeds the surrogate measure consistent with 200,000 individuals, as demonstrated by all prescriptions or sales. The price reduction per dose would be proportional to the increase in demand. This proposal would have particular relevance to those recurrent treatments—some of which will accrue over a lifetime—for which prevalence is a poor predictor of commercial opportunity. While creating a potential disincentive to expand legitimate use of the therapy, such a scheme that creates a reduction in profit margin with increased sales might also encourage industry surveillance of off-label uses for which there is little evidence of effectiveness and/or limit impermissible marketing of unapproved indications, both in order to avoid exceeding the threshold.

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<sup>347</sup> See PREMIER RESEARCH, *THE SCIENCE OF HOPE: THE NEED, THE CHALLENGES AND THREE PROVEN STRATEGIES FOR SUCCESSFUL ORPHAN DRUG DEVELOPMENT 3*, available at [http://premier-research.com/images/uploads/The\\_Science\\_of\\_Hope\\_the\\_need\\_the\\_challenges\\_and\\_three\\_proven\\_strategies\\_for\\_successful\\_orphan\\_drug\\_development.pdf](http://premier-research.com/images/uploads/The_Science_of_Hope_the_need_the_challenges_and_three_proven_strategies_for_successful_orphan_drug_development.pdf). For example, the FDA has exercised flexibility with regard to surrogate endpoints, where the natural histories of rare disease are often unclear. See generally, Aaron S. Kesselheim et al., *Characteristics of Clinical Trials to Support Approval of Orphan vs Nonorphan Drugs for Cancer*, 305 J. AM. MED. ASS'N. 2320, 2326 (2011).

<sup>348</sup> See Steven Simoens, *Pricing and Reimbursement of Orphan Drugs: the Need for More Transparency*, 6 ORPAHNET J. RARE DISEASES 2011, available at <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3132155/>; see also Brian P. O'Sullivan et al., *Pricing for Orphan Drugs: Will the Market Bear What Society Cannot?*, 310 J. AM. MED. ASS'N 1343 (2013).

In either threshold scenario, the limitations could run concurrently with the duration of any ongoing orphan incentives received. If growth in sales or prescriptions were to near the limit of unprofitability, manufacturing incentives could be entertained. However, this recommendation might perversely encourage higher initial costs, if a company were to protect against future reduction in prorated revenue by inflating the initial profit margin. Ultimately, the opportunity in the orphan space must be equivalent to the wider pharmaceutical and biotechnology industries, in order to maintain appeal. As such, and as ever, the orphan-drug incentives together with projected revenue must approximate the profit potential in the wider market.

Potential ideas that ought to be explored, in lieu of wider application of the ODA, are tax credits or subsidies for industry-sponsored access programs to avoid direct and unquantifiable pass-through costs, targeted investment in manufacturing capacity, and stratification of price depending on use.<sup>349</sup> Other ideas that have been proffered include waivers from antitrust laws to allow payors to negotiate collectively to reduce drug cost<sup>350</sup> and value-based insurance reimbursement for drugs.<sup>351</sup> Still others have proffered notions of social and distributive justice.<sup>352</sup> While certainly the collaboration between patient advocacy groups and industry have blurred these lines, dictates of shareholders and profit maximization are innately inconsistent with applicability of such notions to corporations as currently constructed. Of note, Washington and other states have devised social purpose corporations (also known as benefit or B corporations), which provide a legal basis to consider philanthropic motives for corporate decision-making.<sup>353</sup> Such corporate structures may prove better suited for the pharmaceutical and biotechnology industries.

Still, despite concerted effort from all stakeholders to streamline drug development, the healthcare system may yet not be able to withstand what the market has thus far tolerated.<sup>354</sup> In that calculus, market exclusivity should not be conferred to products already available on the market, where already used for the specific indication

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<sup>349</sup> Kesselheim et al., *supra* note 216. Under such a paradigm—though potentially difficult to track at present—products prescribed for approved indications could command a premium price, with lower prices for off-label uses. *Id.*

<sup>350</sup> *Id.*

<sup>351</sup> Michael Drummond, *The Move to Value-Based Pricing for Prescription Drugs*, XONOMY (Dec. 21, 2011), <http://www.xconomy.com/national/2011/12/21/the-move-to-value-based-pricing-for-prescription-drugs/>; see also DELOITTE, VALUE-BASED PRICING FOR PHARMACEUTICALS: IMPLICATIONS OF THE SHIFT FROM VOLUME TO VALUE 1 (2012), available at <http://deloitte.wsj.com/cfo/files/2012/09/ValueBasedPricingPharma.pdf>.

<sup>352</sup> Rai, *supra* note 168, at 256.

<sup>353</sup> See WASH. REV. CODE § 23B.25 (2010); *Social Purpose Corporation*, OFFICE OF THE SECRETARY OF STATE, <http://www.sos.wa.gov/corps/SocialPurposeCorporation.aspx>.

<sup>354</sup> O'Sullivan et al., *supra* note 348.

for which approval is sought and, particularly, where publicly funded research would be used to support the application.<sup>355</sup> In such circumstances, the manufacturer's reinvigoration of a possibly lagging health technology under the watchful eye of the FDA is an inadequate contribution for such public investment and private reward. Rather, such instances should be viewed through the prism of a manufacturing deficiency and incentivized accordingly. While incentives to manufacture existing drugs for known but unprofitable indications may be needed, the ODA—and market exclusivity, particularly—is not the appropriate mechanism to achieve this result. Alternative methods to spur production of non-profitable but necessary drugs, such as methotrexate, should be considered.<sup>356</sup>

If, without a new pricing structure in the future, market exclusivity does create rampant monopolies and exorbitant costs through repurposing, as more diseases are sub-classified by genotype, it may become necessary to reduce the statutory threshold for orphan-drug designation or, in contravention of the recent final rule, to limit application of the ODA to only those diseases with a prevalence of 200,000—effectively eliminating qualification based on an orphan subset of a disease with a prevalence greater than 200,000. While disaggregation of more pervasive diseases based on pharmacogenomics serves the economic purpose of the ODA,<sup>357</sup> the dramatic increase in products amenable to orphan designation—marketing exclusivity and monopoly pricing therefor—may accelerate the cost curve and prove an unsustainable model.

Pharmacogenomics, and personalized medicine more generally, may create the new orphans. If the panoply of therapies is to become increasingly diverse based on the particular needs of smaller and smaller cohorts of individuals, an increasing number of products will require manufacture.<sup>358</sup> Rarity negating profitability will no longer be

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<sup>355</sup> See *Orphan Drugs*, BIO, *supra* note 83.

<sup>356</sup> Linda A. Johnson, *Methotrexate Shortage: Doctors Urge More Production Of Scarce Cancer Drug*, HUFFINGTON POST (Feb. 13, 2012), [http://www.huffingtonpost.com/2012/02/14/methotrexate-shortage-scarce-cancer-drug\\_n\\_1276304.html](http://www.huffingtonpost.com/2012/02/14/methotrexate-shortage-scarce-cancer-drug_n_1276304.html). Interestingly, some have suggested that Congress look to the ODA as the template in drafting legislation that will incentivize drug manufacturing for unprofitable generics. See Letter from Brian M. Rosen, Senior Vice President of Public Policy, Leukemia & Lymphoma Society, to Leslie Kux, Assistant Comm'r for Policy, U.S. Food and Drug, Admin., (Mar. 14, 2013) available at [http://www.lls.org/content/nationalcontent/pdf/ways/LLS\\_Comments\\_to\\_FDA\\_re\\_shortages\\_3\\_14\\_13.pdf](http://www.lls.org/content/nationalcontent/pdf/ways/LLS_Comments_to_FDA_re_shortages_3_14_13.pdf). However, market exclusivity would only delay the concern for a period of time, assuming no alternative treatment is found in the interim.

<sup>357</sup> Though, it could be argued that the intent of the ODA is best served by targeting drug development for those truly rare diseases which have historically affected so few individuals as to be unprofitable, as opposed to predominantly supporting cancer therapeutics—cancers being much more pervasive generally.

<sup>358</sup> Valerie Castle & Matthew Davis, *New Prescriptions for Shortages of Vital Drugs*, U. OF MICH. HEALTH BLOGS (Mar. 12, 2012), <http://uofmhealthblogs.org/childrens/voices-from-mott/new-prescriptions-for-shortages-of-vital-drugs/827/> (last visited Apr. 13, 2014).

the determinant limitation but, rather, capacity will be challenged.<sup>359</sup> Will the market be able to accommodate the diversity with sufficient production capacity or will governments, patients, and advocacy groups be left to find new methods to incentivize inclusion in a market saturated with medications for diseases with a prevalence less than 200,000 individuals? The recent rise of biotechnology companies certainly portends the beginning of this trend.

The current tenor of optimism surrounding the development of orphan products stems from greater collaboration between the various stakeholders, with a patient-centric focus.<sup>360</sup> The FDA, patients, patient advocacy groups, payors, academia, and life-sciences companies have begun a concerted effort for earlier engagement and consistent communication.<sup>361</sup> Such a complement of resources will create efficiencies, and more significant buy-in will go a long way to ameliorate what have been very entrenched and counterproductive attitudes. Still, it remains to be seen whether a more inclusive, and yet more individualized, healthcare industry in the U.S. can accommodate the diversity while transitioning to a system that ensures affordable access to sustained innovation.

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<sup>359</sup> Patrick Rajan, *Personalized Medicine: Targeting a Market of One*, FROST & SULLIVAN (May 19, 2004), <https://www.frost.com/sublib/display-market-insight.do?id=19196998> (“Manufacturing capacity will have to be ramped up since biomanufacturing facilities are scarce and can take up to five years to become fully operational.”); see also THE BIOBUSINESS OF MINNESOTA AND DELOITTE CONSULTING LLP, DESTINATION 2025: FOCUS ON THE FUTURE OF THE BIOLOGIC AND BIOPHARMACEUTICAL INDUSTRY 23 (2009), [http://www.biobusinessalliance.org/Files/531111\\_d2025\\_whitepaper\\_biopharmaceuticals\\_biologics\\_smaller\\_secured.pdf](http://www.biobusinessalliance.org/Files/531111_d2025_whitepaper_biopharmaceuticals_biologics_smaller_secured.pdf) (“With the demand for biotechnology products rising, manufacturing capacity has become scarce . . .”); Reducing Prescription Drug Shortages, Exec. Order No. 13,588, 76 Fed. Reg. 68,295, (Oct. 31, 2011), available at <http://uscodebeta.house.gov/view.xhtml?sessionid=559E25FA7CC7A047272812BA291CABD3?req=granuleid%3AUSC-prelim-title21-chapter9-subchapter5&saved=%7CZ3JhbnVsZWlkOIVTQy1wcmVsaW0tdGl0bGUyMS1zZWNoaW9uMzU5%7C%7C%7C0%7Cfalse%7Cprelim&edition=prelim> (“An important factor in many of the recent shortages appears to be an increase in demand that exceeds current manufacturing capacity.”); see also Angelo De Palma, *Making Medicine Personal*, BUFFALO NIAGARA ENTERPRISE, (Aug. 2007), [http://buffaloniagara.org/About\\_BNE/PressRoom/2007Archive/August/MakingMedicinePersonal](http://buffaloniagara.org/About_BNE/PressRoom/2007Archive/August/MakingMedicinePersonal).

<sup>360</sup> See U.S. FOOD & DRUG ADMIN., REPORT TO CONGRESS, IMPROVING THE PREVENTION, DIAGNOSIS, AND TREATMENT OF RARE AND NEGLECTED DISEASES 5–6 (Mar. 2011), <http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM266374.pdf>. But see Anusha Kambhampaty, *Big Pharma Not Yet Ready to Adopt Orphan Companies*, FINANCIAL TIMES (Sept. 23, 2013), <http://www.ft.com/cms/s/2/502d775a-2489-11e3-8905-00144feab7de.html#axzz2ozfVkJmIw> (citing current and former executive vice presidents of NPS and BioMarin, “[t]he patient focus of orphan drug development is a major point of difficulty for big pharma . . . Culturally, it will be difficult for big pharma to get into the orphan space, as there is an aspect of social work . . . Orphan drug developers get to know each individual patient they are treating, which is much different than the big pharma model . . .”).

<sup>361</sup> Brewer, *supra* note 41 (describing the importance of university, industry partnerships).