

Orphan Drug Policies: Implications for the United States, Canada, and Developing Countries

*Richard Y. Cheung , Jillian C. Cohen and Patricia Illingworth**

Introduction

The United States' *Orphan Drug Act* ("ODA") has been hailed as "one of the most successful US legislative actions in recent history".¹ Although many countries, and governing bodies, have enacted Orphan Drug legislation in the past decade, the United States (US) was the first country to implement an official policy, primarily because of public pressure due to the lack of treatment options for rare disease sufferers in the US. For everyone who has espoused the virtues of the ODA in encouraging research into rare disease treatments, there are equal numbers of detractors who claim that it is a policy that serves mainly to promote private industry by allowing companies to charge outrageous prices for products that rare disease sufferers have no option but to purchase. While these are wildly divergent opinions, the true value of the ODA likely resides somewhere in between.

This paper will provide some background on the history of drug development leading up to the enactment of the ODA. The US ODA will be described in brief detail outlining the incentives structure the ODA provides. The successes and limitations of the ODA, since its inception will be examined and comparisons will be made with other jurisdictions, where relevant. The issue of potentially applying ODA concepts to resolve the drug development gap that presently exists for neglected diseases in developing countries will also be considered. Finally, policy recommendations that could help reconcile some of the perceived deficiencies of the ODA will be put forth. In addition, final perspectives will be presented.

2.0 Creation of Orphans

The late 1950s and early 1960s were marred by the infamous thalidomide tragedy.² Thalidomide was a drug that was prescribed to pregnant women to alleviate symptoms associated with morning sickness. However, when taken during the first trimester of pregnancy it affected the proper growth of the fetus, resulting

*Richard Y. Cheung, PhD, is a first-year law student at the University of Western Ontario, London, Ontario; Jillian C. Cohen is an Assistant Professor at the Leslie Dan Faculty of Pharmacy, University of Toronto, and Patricia Illingworth is an Associate Professor, Department of Philosophy and Religion, Northeastern University, Boston, Massachusetts. Correspondence: e-mail: jillianclare.cohen@utoronto.ca

¹Marlene E. Haffner, Janet Whitley & Marie Moses, "Two Decades of Orphan Product Development" (2002) 1:10 *Nature Reviews* 821, at 821.

²*Ibid.*

in significant birth defects in thousands of children worldwide. Tragic incidents such as this led to the passage of the *Kefauver-Harris Bill* in the US; although thalidomide was never approved in the US market largely because of the circum-spection of Frances Kelsey, a drug evaluator of the Food and Drug Administration (FDA) at the time.³

The *Kefauver-Harris Bill* amended the federal *Food, Drug and Cosmetic Act* (1962) by requiring all drugs to be proven safe and effective by adequate well-controlled studies before being approved for the US market.⁴ While this improved public protection from potentially dangerous pharmaceuticals, it also dramatically increased the costs associated with drug development. Consequently, pharmaceutical companies began to focus on developing treatments for common diseases with large potential markets in order to maximize the possibility of recouping research and development costs and generating significant revenues. As a result, rare diseases were largely ignored because of limited profit motive, hence, becoming "orphaned".

Pursuant to the Kefauver-Harris amendments, the development gap between drugs for common versus rare diseases widened to the point where either very few or no treatment options were available for some disease conditions (e.g. Crohn's disease, Hansen's disease, etc.).⁵ The worsening situation mobilized rare disease sufferers, as they worked aggressively to draw attention to the lack of treatment options available.⁶ Patient advocacy groups continue to be the driving force behind the enactment of orphan drug legislation. Not only did they play a significant role in the US in the early 1980's, but following the US example in the late 1990s, groups like Eurordis (European Organization for Rare Diseases modeled after the US based National Organization for Rare Diseases or NORD) also successfully lobbied in the EU for the enactment of an orphan drug policy.

3.0 United States Orphan Drug Act

The plight of rare disease sufferers became a significant public issue in the late 1970s to early 1980s. The US government was subject to pressure from non-governmental organizations like NORD. Interestingly, NORD's issue became a cause celebre when the actor Jack Klugman took an interest in the issue and helped promote the passage of the ODA into law.⁷ The star of a popular television medical drama at the time, Klugman devoted episodes of his show to rare disease issues.

³Teri Randall, "Thalidomide has 37-Year History" (1990) 263:11 *Journal of the American Medical Association* 1474.

⁴*Supra* note 1 at 821.

⁵John Henkel, "Orphan Drug Law Matures into Medical Mainstay" (1999) *FDA Consumer* 33:3 (May-June 1999) 29 at 30.

⁶*Supra* note 1 at 821.

⁷John Henkel, "How TV Launched the Orphan Drug Law" *FDA Consumer* 33:3 (May-June 1999) 34 at 34.

This led to a huge outpouring of public support that the US government could not ignore.

On January 4, 1983, then President Ronald Reagan signed the ODA into law.⁸ Drugs, vaccines, and diagnostic agents would now qualify for orphan status if they were intended to treat a disease group with a prevalence of less than 200,000 US citizens. In order to encourage the development of drugs for orphan diseases, the ODA included a number of incentives including: (i) seven-year market exclusivity for firms that developed orphan drugs; (ii) tax credits equal to half of the development costs — later amended to offer a fifteen-year carry-forward provision and a three-year carry-back stipulation that can be applied in profitable years; (iii) drug development grants; (iv) fast-track development and approvals of drugs indicated for rare diseases; (v) expanded access to the Investigational New Drug Program, which allows patients access to pre-approved orphan drugs; and (vi) fee reductions, whereby the US FDA waives its drug application fees.⁹

Market exclusivity is particularly appealing to pharmaceutical firms as an incentive to pursue orphan drug development. The seven-year market exclusivity period differs from traditional patent law in that it does not begin until the drug is granted FDA approval and is independent of the drug's current patent status. Furthermore, if a market competitor wishes to introduce a drug for the same indication, the onus is on the competitor to prove that their drug is therapeutically superior (e.g. increased efficacy, less toxicity, etc.) when compared to the present drug indicated for the rare disease of interest. This incentive creates an attractive monopolistic market for companies interested in developing a product for any given rare disease.¹⁰

4.0 Success of the US Orphan Drug Act

4.1 A Star is Born

There are an estimated 6000 rare diseases worldwide. In the US alone, it is thought that upwards of 25 million people suffer from rare diseases.¹¹ In the absence of an incentive structure that encourages the development of treatments for rare diseases, a significant percentage of the US population, as well as in other countries

⁸ *Ibid.*

⁹ Marlene E. Haffner, "Orphan Drugs: the United States Experience" (1999) 33 Drug Information Journal 565.

¹⁰ Carson R. Reider, "The Orphan Drug Act: Provisions and Considerations" (2000) 34:1 Drug Information Journal 297 [Reider]; Lisa Ruby Basara & Michael Montagne, *Searching for Magic Bullets* (New York: Pharmaceutical Products Press, 1994) at 144-146 [Basara].

¹¹ Thomas Maeder, "The Orphan Drug Backlash" (2003) 288:5 Scientific American 80 at 81.

throughout the world, would not have treatments for their diseases. This further underscores the moral and health significance of the ODA.

Before its enactment in 1983, only ten products for the treatment of rare diseases were approved for use in the US.¹² Since then, over 1,100 medicinal products have received orphan status in the US, with 248 of these products gaining approval by the FDA.¹³ This increase in drug development has benefitted countless sufferers of rare diseases by introducing products that have both improved the quality of life of orphan disease patients and extended life expectancies. Not only has this legislation helped patients, but it has also benefitted the health care system through cost-savings because many of the treatments help to avoid expensive surgeries and their incidental costs.¹⁴

Cystic fibrosis (CF) is a good example of a designated orphan disease. In the 1980s, CF patients rarely lived beyond their early teens — their brief lives marked by repeated lung infections. However, drugs like Pulmozyme and Tobramycin, both developed with aid from the ODA, revolutionized treatment for CF patients by significantly improving their quality of life and extending their life expectancies. Now, CF patients often survive into their thirties and some into their fifties.¹⁵ These stories are commonplace now in large part due to the success of the ODA.

In 2002, President George W. Bush signed the *Rare Diseases Act* into law.¹⁶ This bill amended the *Public Health Service Act* in the US to establish an official Office of Rare Diseases having federal powers. It also increased funding for the development of treatments for patients with rare diseases. This was a significant event in that it re-affirmed the growing importance of orphan disease issues.

A number of cases have surfaced in the U.S. courts that reflect the high value pharmaceutical and biotech companies place on securing orphan drug designation, and in particular, on the seven-year period of market exclusivity. Although the ODA does not limit the number of drugs that may be designated for a specific orphan disease, if an orphan drug has received market approval first, then the FDA is not permitted to confer orphan drug status on another drug until after the seven-year period.¹⁷ Second, similar drugs can win orphan drug designation only if it can be shown that the second drug is clinically superior to the marketed drug.¹⁸

¹² *Supra* note 1 at 824.

¹³ Carol Rados, "Orphan Products: Hope for People with Rare Diseases" *FDA Consumer* 37.6 (November-December 2003), online: U.S. Food and Drug Administration <http://www.fda.gov/fdac/features/2003/603_orphan.html>.

¹⁴ *Supra* note 11 at 81.

¹⁵ *Supra* note 5 at 29.

¹⁶ Alexander Iribarne, "Orphan Diseases and Adoptive Initiatives" (2003) 290:1 *Journal of the American Medical Association* 116.

¹⁷ Robert A. Bohrer & John T. Prince, "A Tale of Two Proteins: The FDA's Uncertain Interpretation of the Orphan Drug Act" (1998-1999) 12 *Harv. J.L. & Tech.* 365 at 371.

¹⁸ *See* 21 U.S.C. § 360bb (1997), *see also* 21 C.F.R. § 316.20(a) (1999).

Only the first manufacturer to receive full FDA approval, including pre-clinical studies on laboratory animals and clinical investigation receives exclusivity. The two exceptions to the exclusivity rule are first, when the exclusivity holder cannot provide adequate amounts of the drug and second, the exclusivity holder consents to it.¹⁹ Obviously, given what is at stake with orphan drug designation, especially the promise of market exclusivity, the question of what will count as the same vs. a different drug is important. Indeed, much of the litigation in this area is over this question.

In *Genentech, Inc. v. Bowen*, 676 F. Supp. 301 (D.D.C. 1987), the ODA's definition of "different" was at issue. Genentech had been granted market exclusivity for Protropin, a genetically engineered human growth hormone, helpful in treating hypopituitary dwarfism. Shortly after, Eli Lilly was given market exclusivity under the ODA for Humatrope, a human growth hormone, that differed from Protropin only with respect to one amino acid. Genentech objected on the grounds that for purposes of the ODA, Humatrope was the same as Protropin and therefore ineligible for market exclusivity. The U.S. District Court for the District of Columbia held that the two were not the same under the ODA but it refused to state a rule for determining when two drugs are different.²⁰

The same question arose in *Amgen, Inc. v. Chugai Pharm. Co.*²¹ Amgen had received orphan drug exclusivity for Epogen, for the treatment of chronic anemia associated with end stage renal disease. Soon after Chugai attempted to secure orphan drug designation for Marogen, arguing that its glycosylation pattern differed from Amgen's Epogen. Eventually Amgen won the dispute. At first the FDA settled on a definition of "same drug" that specified that a second drug would be considered the same as the first drug if it has the same "molecular structural features" and was intended for the same use. However, if the second drug was "clinically superior," then it would be considered different.²² There were three ways that clinical superiority could be shown: greater effectiveness, greater safety and evidence that the drug can make an important contribution to unusual cases.²³

Additional queries concerning this definition arose when the FDA decided that interferon α , found in Chinese hamster ovaries, and interferon α found in *E. coli* were different and could both be approved for the treatment of multiple sclerosis. Berlex Laboratories, the producer of Betaseron, the *E. coli* produced drug, disagreed with the FDA's decision to approve Avonex and sought to have the decision reversed. In *Berlex Laboratories Inc v. FDA*,²⁴ the court found that Avonex was clinically superior to Bateseron. Among the differences between the two is the

¹⁹ *Supra* note 17 at 373.

²⁰ *Ibid.* at 388.

²¹ *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200 (Fed. Cir. 1991).

²² See 21 C.F.R. § 316.3(b)(3)(ii) (1999).

²³ See *ibid.* at § 316.3(b)(3)(i)-(iii).

²⁴ *Berlex Laboratories, Inc. v. FDA*, 942 F. Supp. 19 (D.D.C. 1996).

number of times each must be injected. Bataseron must be injected every other day, while Avonex is injected once a week.

In 2001, the same-drug question was raised again with respect to the cancer drugs, Paxene and Taxol. Baker Norton developed Paxene and BMS, Taxol. In March of 1997, Baker Norton submitted a new drug application for Paxene and sought orphan drug designation for its treatment of Kaposi's sarcoma, a rare disease. It received that status on April 15, 1997. Similarly, BMS sought orphan designation for Taxol for the treatment of Kaposi's in January of the same year and was granted that designation by the FDA.²⁵ In this race for orphan drug designation, whichever drug was first approved would receive market exclusivity. The FDA notified Baker Norton that it had determined that Paxene was safe and effective, but could not give final approval until after Taxol's period of exclusivity. It also stated that Baker Norton could receive final approval for marketing before this date if it could show that Paxene and Taxol are not the same drug. Baker Norton responded with a complaint against the FDA in which it claimed that "the regulation itself is contrary to law, because the FDA's interpretation of the word "drug" is contrary to unambiguous legislative intent, or, alternatively, that its interpretation is unreasonable and impermissible."²⁶ The complaint alleged that the FDA wrongly interpreted the term "drug" to encompass only the active ingredient rather than the entire drug product and that its refusal to grant final approval of Paxene were "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law."²⁷ In count II, it claimed that the FDA exceeded its statutory discretion when it refused to grant approval for Paxene. Most of the case consisted of an analysis of the permissibility of the FDA's interpretation of the term "drug." The court found that the FDA's interpretation was permissible and consistent with the purpose of the Orphan Drug Act. What this brief overview of some of the key cases in this area shows is that the Orphan Drug Act's offer of market exclusivity in exchange for the development of products that will treat orphan disease is indeed prized by the pharmaceutical community.

4.2 "Imitation is the sincerest form of flattery"

To further underscore the importance of the US legislation, in 1993 and 1999 respectively, Japan and the EU each passed orphan drug legislation. While Japan and the EU essentially copied the tried and tested US orphan drug model, differences do exist. Australia and Singapore have also instituted limited orphan drug policies that have benefited rare disease patients in their respective countries. To date, Canada has not implemented an official orphan drug policy, choosing instead to rely on a combination of access mechanisms to procure orphan drugs for its rare disease sufferers.

²⁵ *Baker Norton Pharmaceuticals, Inc., v. FDA*, 132 F. Supp. 2d 30 (D.D.C. 2001).

²⁶ *Ibid.* at 33.

²⁷ *Ibid.* (quoting the *Administrative Procedures Act*, 5 U.S.C. § 706(2)(A) (2000)).

4.2.1 Japan

The disease prevalence limit for the classification as an orphan disease in Japan is set at less-than 0.04% of the country's population, a lower level than both the US and EU which place the limit at 0.1% of their respective populations. Successful orphan drugs are also granted ten-years of market exclusivity, compared to seven-years in the US. Furthermore, before drugs are granted orphan status in Japan, they must have a reasonable assurance of successful development. One of the most unique inclusions in the Japanese legislative regime is the stipulation that mandates companies to pay a one-percent sales tax on orphan drugs that have annual profits exceeding \$100 million yen until such time as government subsidies received by the firm have been repaid.²⁸

4.2.2 European Union

Throughout the 1990's, the European Commission, the legislative body of the EU, displayed increasing interest in issues surrounding orphan drug development — partly in response to mounting pressure from organized rare diseases advocacy groups (e.g. Eurordis). Prior to the EU's enactment of an orphan drug policy in 1999, none of the member countries had explicit orphan drug legislation. However, some countries, including the United Kingdom, France, and Sweden had broad national drug policies that encompassed and encouraged orphan drug development.²⁹ These policies generally included incentives for drug development in the form of regulatory and application fee reductions, as well as programs to facilitate access to orphan drug medications.

Like Japan, the EU gives approved orphan drugs a ten-year market exclusivity period. While the EU does not provide companies with tax credits due to the differences in tax structures between member nations, sponsor companies are still able to obtain tax benefits by negotiating with individual countries. The EU charged the London-based European Agency for Evaluation of Medicinal Products (EMA) with administering the mandate of its legislation, amongst other responsibilities. The significance of the EMA is that it is a cost-saving mechanism for both EU member nations and orphan drug sponsor companies because it streamlines the application and approval process. EU legislation also provides incentives for companies developing products for diseases occurring mainly in tropical regions. Recently, in an effort to curtail any possible exploitation of orphan drug incentives by drug companies, the EU amended its legislation requiring that all orphan drugs be stripped of their orphan status after five-years if they are considered to be "extraordinarily profitable".³⁰

²⁸ Makoto Shiragami & Kiyohito Nakai, "Development of Orphan Drugs in Japan: Characteristics of Orphan Drugs Developed in Japan" (2000) 34:3 Drug Information Journal 839; Mae Thamer & Niall Brennan, "A Cross-National Comparison of Orphan Drug Policies: Implications for the U.S. Orphan Drug Act" (1998) 23:2 J. Health Pol. 265 at 280 [Thamer].

²⁹ Thamer, *ibid.* at 273.

³⁰ Jean Lang & Susan C. Wood, "Development of Orphan Vaccines: An Industry Perspective" (1999) 5:6 Emerging Infectious Diseases 749; *Supra* note 11 at 83.

4.2.3 Australia and Singapore

Other countries that have also adopted specific orphan drug legislation include Singapore and Australia. Singapore's legislative regime, which came into operation at the end of 1991, sets up a definition of orphan drugs and provides a legal framework for imports into Singapore.³¹ Australia adopted its orphan drug policy in 1997. With the help of the US FDA, the Therapeutic Goods Administration developed specific orphan drug legislation largely based on the US model and the FDA's experience with it. The incentives of the Australian program are fee waivers and priority evaluation. It does not offer market exclusivity, tax credits, or grants.³²

4.2.4 Canada

Canada has no official policy for orphan drugs, possibly stemming from a combination of low relative levels of innovative drug research, reliance on the US market, and a small population. Fortunately, Canada does have systems in place that enable rare disease sufferers to obtain necessary drugs when required.³³ One such mechanism is the Special Access Program, which allows for the emergency release of drugs otherwise unavailable for sale in Canada. Although the program is good in intent, it is often inefficient and has a number of bureaucratic obstacles. In terms of stimulating orphan drug development, companies that undertake orphan drug development are eligible to receive research and development tax credits, qualify for protection that Canada's strong patent laws provide, and are entitled to a reduction in the new drug application fees offered through the Therapeutic Products Directorate (TPD).

In 1996, TPD, known as the Drug Directorate at the time, investigated the rare disease issue in Canada and concluded that: (i) all orphan drugs approved in the US, at the time of the report, were available in Canada; (ii) the high costs of orphan drugs could be an obstacle to patient access; and (iii) the Canadian population was not large enough to support significant research and development in the area. Their recommendation was that no orphan drug policy was needed since Canadians already had access to orphan drugs.³⁴

In an era of diminishing resources, an official orphan drug policy for stimulating the development of orphan drugs in Canada can be viewed as unnecessary given the relative paucity of innovative drug research that is presently conducted in Canada. On the other hand, it could encourage greater investment in

³¹ European Union, Scientific and Technical Options Assessment, *Orphan Drugs* (March 1999), online: European Parliament <http://www.europarl.eu.int/stoa/publi/167780/chap3_en.htm>.

³² Austl., Commonwealth, Department of Health and Aged Care, *the Orphan Drug Program and Improving Community Access to Effective Drugs for Rare Diseases*, (Canberra: Australian Government Publishing Service, December 2001) at 38.

³³ Canada, Health Canada, *Orphan Drug Policy* (Ottawa: Drugs Directorate, 27 November 1996) at 9.

³⁴ *Ibid.* at 20.

research and development by the pharmaceutical industry in Canada. While the prospect of forging a strong biotechnology sector in Canada is enticing, it does not address the immediate needs of orphan disease sufferers in the country. Given the importance of providing life-saving or life-enhancing products to those in need, we propose that a policy be developed that focuses on improving access of these treatments to Canadian sufferers of rare diseases through the establishment of a Canadian National Office of Rare Diseases. Both physicians and rare disease sufferers often argue that it is difficult to find current information on rare diseases and their available treatment options.³⁵ Not only could a central office serve to disseminate important information on rare diseases, but it could also facilitate access to orphan drugs by providing funds to help patients purchase expensive treatment options or even identify individuals who might qualify for clinical trials in Canada or abroad. This is a practical policy solution that ideally will not demand much in the way of human and financial resources.

Clearly, the success of the US ODA can be measured in myriad ways. It has succeeded in creating incentives for the development of drugs for rare diseases, evidenced by the unprecedented number of drugs and biological agents that have applied for orphan status following the enactment of the legislation. Furthermore, the US orphan drug program has been used as a legislative model for many other countries and has had an impact on shaping policies concerning both access to, and development of, orphan drugs for people with rare diseases. While the provisions of the US ODA may not presently be feasible in some countries (e.g. Canada) for various reasons, this should not deter the development of a focused rare disease treatment strategy. As Australia has shown, through collaboration and a practical assessment of a population's health needs, rare disease sufferers can benefit from even partial application of the US ODA principles.

5.0 Two Sides to Every Coin

5.1 Rich Orphans

While the ODA has been largely successful, there are still some challenges that must be overcome. One of the most common criticisms of the ODA is that it places no restrictions on the prices companies can charge for their products. While the majority of orphan drugs are not very profitable, there are numerous examples of drugs that were developed using orphan drug incentives that have become "blockbuster" products.

Zidovudine (AZT) is a common medication for HIV/AIDS patients and was granted orphan status when AIDS was considered an "obscure disease of the immune system"; however, even when the AIDS epidemic escalated in the US, AZT maintained its orphan designation. In 1997, it earned Glaxo Wellcome, as the

³⁵ Andrew Duffy, "Rare Diseases' Troubling Questions" *Ottawa Citizen* (21 January 2002), A10.

company was known at the time, \$471 million (USF) in revenue.³⁶ This raises the question of whether there should be limitations placed on drug designations as orphan status. However, this could also be viewed as a disincentive for firm investment in orphan diseases.

Erythropoiten (Epogen) is a drug that is used to boost red blood cells in the body. It was granted orphan status based on Amgen's intention to target the end-stage renal failure population — approximately 78,000 patients at the time. However, once on the market, clinicians discovered that it was also useful for boosting red blood cells in cancer and AIDS patients. Thus, the market size for Epogen dramatically increased to the point where the drug now earns Amgen a reported US\$ 2 billion per year in annual revenue.³⁷ Another extraordinarily profitable orphan drug is Cerezyme (Genzyme), a treatment for Gaucher's disease, with annual revenues of US \$500 million.³⁸

Examples such as these have served to fuel the call for reform by ODA critics. The ODA explicitly states that, "a pharmaceutical company which develops an orphan drug may reasonably expect the drug to generate relatively small sales in comparison to the cost of developing the drug and consequently to incur a financial loss".³⁹ From this statement, it would seem that the spirit of the ODA is ostensibly to break down one of the main barriers to orphan drug development — the ability for companies to recover sunk costs. Thus, companies that develop blockbuster orphan drugs are often accused of abusing the system.

While the impact the ODA has had on drug development for rare diseases is not in question, critics have lobbied for reform claiming that the incentive structure is excessively generous. They argue that the lack of price controls coupled with vague definitions of orphan diseases encourage an inflationary market.⁴⁰ While financial aid programs are available to help rare disease sufferers purchase treatments that are otherwise unobtainable due to cost, it is not uncommon to hear stories of patients having to sell their homes and spend their life-savings simply to qualify for government or corporate assistance programs.⁴¹ This lack of price control defeats the purpose of the legislation which is to ensure that those patients that need life-saving or life-enhancing products have access to them. While some third party insurance payers offer coverage for orphan drugs, the high costs associated with some treatments often lead to situations where either the premiums become

³⁶"Safety in Numbers" *The Economist* 64 347:8070 (30 May 1998); Susannah Motl, Sarah J. Miller & Patrick Burns, "Programs Established by FDA to Expedite Patient Access to Medications" (2003) 60 *American Journal of Health System Pharmacy* 339.

³⁷"Safety in Numbers", *ibid.* at 64.

³⁸Brian Reid, "New Products Highlight Ambiguity of Orphan Drug Law" (2003) 21 *Nature Biotechnology* 6 at 7.

³⁹*The Orphan Drug Act of 1983*, Pub. L. No. 97-414, 96 Stat. 2049 (codified at 21 U.S.C. § 360aa-360ee).

⁴⁰A.M. Garber, "Benefits versus profits: has the orphan drug act gone too far?" (1994) 5:2 *PharmacoEconomics* 88.

⁴¹*Supra* note 11 at 83.

extraordinarily high, or the lifetime maximum for the plan is exceeded whereupon the coverage is revoked.⁴²

Proponents for reform of the US orphan legislation assert that the high cost of orphan drugs is unethical because rare disease patients have no alternative treatment options. They are placed in a morally reprehensible situation. This has prompted many to label the ODA as nothing more than a “Biotechnology Promotion Act”⁴³, as it has spawned a considerable biotechnology industry that has been allowed to flourish from sales of highly priced products in a monopolistic market — largely due to the incentives offered by the Act. Critics assert that it is unjust when private companies use public monies to develop blockbuster drugs without reimbursement. Furthermore, they argue that the US prevalence limit for orphan disease designation is too generous; unconvinced that a drug will be unprofitable simply because its target indication has a patient population of less than 200,000 patients.⁴⁴

5.2 A Growing Call for Change

While reforms have been proposed in the past, they have repeatedly been voted down in Congress or vetoed by the incumbent US President, likely due to the enormous influence that the research based pharmaceutical industry has on political decision makers in the United States. Some of the more popular reform proposals include: (i) having an orphan drug forfeit its status, and the accompanying incentives, if the size of the patient population it serves grows beyond 200,000;⁴⁵ (ii) employing a “sales trigger” whereby a drug loses its orphan designation if the cumulative revenue it generates exceeds a predetermined target within the seven-year market exclusivity window;⁴⁶ and (iii) shortening the length of market exclusivity to four-years with an opportunity for a three-year extension (seven-years total) if the drug is proven to be truly unprofitable.⁴⁷ While the merits of each of these proposals have been extensively discussed in literature,⁴⁸ the emergence of pharmacogenomics has strengthened the commonly held belief that the ODA cannot continue unaltered.

Pharmacogenomics holds the possibility of targeting a drug therapy to an individual based on that patient’s genetic sequence — individualized drug therapies.⁴⁹ Until recently, pharmaceutical companies have “relied on mass sales of

⁴² Reider, *supra* note 10 at 298; *Supra* note 28 at 83.

⁴³ *Supra* note 28 at 80.

⁴⁴ Thamer, *supra* note 28 at 269.

⁴⁵ Basara, *supra* note 10 at 157.

⁴⁶ *Ibid.*

⁴⁷ Thamer, *supra* note 38 at 271.

⁴⁸ Basara, *supra* note 10 at 143-159.

⁴⁹ Arti K. Rai, “Pharmacogenetic Interventions, Orphan Drugs, and Distributive Justice: the Role of Cost-benefit Analysis” (2002) 19:2 *Social Philosophy & Policy* 246; Haffner, *supra* note 1 at 824.

identical drugs to large, poorly differentiated patient populations.”⁵⁰ However, with advances in pharmacogenomics, what is now considered and treated as a homogeneous disease may in fact be an aggregate of different genetic sequences, each with different responses to any given drug therapy.⁵¹ This will have many potential consequences within the drug development community. On one hand, it could improve overall drug development and therapy since drug efficacy will be demonstrated faster and less expensively, as companies will be able to target drugs exclusively to patients who will respond favourably. However, it could also be reasoned that using pharmacogenomics to sub-divide disease populations based on genetics will lead to the formation of groups with less than 200,000 patients — creating orphan diseases that did not previously exist. While resource limits have not been considered to date, a significant increase in the number of designated orphan products would put considerable strain on limited resources. It also suggests that these patient groups may very well be subject to high drug prices.

While the proper course of action continues to be heatedly contested by representatives from all parties, the need for reform of the ODA is apparent. Although the ODA has undoubtedly served its purpose, the current US legislation was conceived and written in 1983. Recent scientific advances, coupled with the burgeoning biotechnology industry and the high prices associated with some of the drugs that these companies produce, are justifications for reforms which reflect the current and ever-changing drug development landscape. However, the call for reform of the ODA should be tempered by the fact that any changes to the incentive structure of the legislation may negatively impact on the degree to which companies may be willing to invest into rare disease research. While, the EU and Japan have both included clauses in their respective policies that strip profitable orphan drugs of their incentives, the level of drug development in these countries is minor relative to the US industry. After all, it has been the generous incentive structure of the ODA that has made the initiative so successful to-date.

6.0 Applicability of Principles of the ODA to Tropical Diseases?

Even though developing countries represent about 80 percent of the global population, they represent a relatively small proportion of the global pharmaceutical market in value (about 20 percent of the global value),⁵² thus providing limited market incentives for the development of new drugs specific to diseases endemic to those countries (including many tropical diseases). Since 1973, more than twenty-five new infectious diseases have emerged, all requiring treatment with

⁵⁰ *Supra* note 11 at 84.

⁵¹ *Supra* note 1 at 824.

⁵² Daniel Berman & Suerie Moon, “Fatal Imbalance: The Crisis in Research and Development for Drugs for Neglected Diseases” (Geneva: Médecins Sans Frontières Access to Essential Medicines Campaign and the Drugs for Neglected Diseases Working Group, September 2001) at 8.

pharmaceuticals.⁵³ Some like HIV/AIDS are global in their scope and are particularly devastating. Other diseases like cholera, tuberculosis, and malaria are mainly disease burdens of developing states.

Even though global expenditure on health research and development has increased significantly and continues to rise, diseases of the poor are still largely ignored by the pharmaceutical industry. In 2001, an estimated US\$ 70 billion was invested globally in health research and development, with the US private sector alone accounting for just under half of the spending.⁵⁴ An analysis of drug development outcomes over the past 25 years shows that only 15 new drugs were indicated for tropical diseases and tuberculosis.⁵⁵ These diseases primarily affect poor populations and account for 12% of the global disease burden. In comparison, 179 new drugs were developed for cardiovascular diseases, which represent 11% of the global burden of disease.⁵⁶

It is clear that the issue of orphan drugs is not exclusive to developing countries, as even prevalent diseases can be considered orphans. Companies tend to avoid developing drugs for certain disease groups deemed to have small markets because of the uncertainty surrounding their ability to recover investment dollars. Similarly, the pharmaceutical industry avoids developing drugs for diseases in developing countries, not because of the small market, but because of their inability to pay for the drugs.

Market exclusivity is widely regarded to be the most motivating incentive for companies to develop drugs for rare diseases. However, it is unlikely that a similar incentive will stimulate research into tropical diseases. While enforcement of the Trade Related Aspects of Intellectual Property Rights (TRIPS) Agreement in all World Trade Organization (WTO) member countries by 2005,⁵⁷ and finally by 2016, may help to mitigate patent concerns, the lack of purchasing power by developing nations will remain an obstacle. Furthermore, the need to develop production and distribution mechanisms, due to the lack of infrastructure will place further cost pressures on companies.⁵⁸

While the ODA has been largely successful in the US, the specific incentives the ODA offers is unlikely to encourage the same level of development for tropical diseases in developing countries. The EU and the US extend incentives from their

⁵³ Jillian Clare Cohen *et al.*, "Improving Transparency in the Pharmaceutical System: The Case of Costa Rica" (Washington, DC: World Bank, 2002) unpublished paper.

⁵⁴ *Supra* note 11 at 16.

⁵⁵ *Ibid.* at 10.

⁵⁶ *Ibid.*

⁵⁷ Patrice Trouiller *et al.*, "Is Orphan Drug Status Beneficial to Tropical Disease Control? Comparison of the American and Future European Orphan Drug Acts" (1999) 4:6 *Tropical Medicine & International Health* 412.

⁵⁸ Patrice Trouiller *et al.*, "Drug Development for Neglected Diseases: a Deficient Market and a Public-health Policy Failure" (2002) 359:9324 *The Lancet* 2188.

respective orphan drug legislations to include drug development for tropical diseases; however, as of June 2002, no drug candidates for neglected diseases in developing countries have been developed and marketed through these policies.⁵⁹ This drug development gap has led to a number of proposals aimed at fulfilling the needs of patients suffering from neglected diseases.

One potential alternative solution includes initiatives such as public-private partnerships (PPPs), which include collaborations between the private sector (e.g. pharmaceutical companies, philanthropic institutions, etc.) and the public sector (e.g. governments, academia, etc.).⁶⁰ Medicines for Malaria Venture (MMV) and Global Alliance for Tuberculosis (GAT) are examples of two disease-based PPPs that have recently been formed, November 1999 and October 2000 respectively, involving diverse partners such as pharmaceutical industry, academia, and development agencies.⁶¹ MMV and GAT both focus on funding projects that convert promising drug candidates to viable drug treatments using a social venture capital approach.⁶² While the ultimate success of these PPPs is still to be determined, at the very least they provide proof that diverse collaborations are possible.

Another proposal put forth to encourage tropical diseases drug research suggests instituting a regulation requiring a small fraction of industry revenues be sent to developing countries.⁶³ While this proposition may provide recipient nations with more resources to purchase drugs, it does not provide a long-term solution for the drug development gap. Furthermore, pharmaceutical companies will likely compensate for any regulation requiring them to divert money to developing nations by either increasing the price of their products or by inflating their development costs.

In the absence of any change in the global distribution of wealth, any plan to narrow the development gap between drugs indicated for profitable versus neglected diseases will require the support of a third-party since developing countries do not have the resources at hand to offer companies generous incentives. While PPPs are present-day examples of such collaborations that have resulted in some gains, their potential is often muted by the varying agendas of multiple stakeholders.⁶⁴ Strides have been made in developing drugs for some tropical diseases; however, bolder projects are needed if a significant and sustainable impact in drug development is to be realized.

⁵⁹ *Ibid.*

⁶⁰ *Ibid.*

⁶¹ Craig Wheeler & Seth Berkley, "Initial Lessons from Public-private Partnerships in Drug and Vaccine Development" (2001) 79 Bulletin of the World Health Organization 728.

⁶² *Supra* note 58 at 2197; *Ibid.* at 729.

⁶³ Arrigo Schieppati, Giuseppe Remuzzi & Silvio Garattini, "Modulating the Profit Motive to Meet Needs of the Less-developed World" (2001) 358:9293 *The Lancet* 1638.

⁶⁴ *Supra* note 58 at 2197.

7.0 New Directions

7.1 A global approach?

While existing orphan drug policies have been generally praised for their success in providing rare disease sufferers with life-saving treatments, the most commonly cited criticism of the various legislations has been that they promote high drug prices. High orphan drug costs have even been recognized by Canada, a country without an official orphan drug policy, as a barrier to drug access by patients. Abbey Meyers, the president of NORD, claims that to-date, drug costs have not prevented rare disease sufferers from obtaining an orphan drug.⁶⁵ In spite of her assertion, increasingly sophisticated drugs combined with the emergence of pharmacogenomics will continue to inflate drug prices to the point where they will eventually preclude treatment access to patients belonging to lower socioeconomic groups.

The aforementioned Kefauver-Harris amendments required that all drugs be proven safe and effective by well-controlled studies. “Well-controlled studies” often require hundreds, if not thousands, of patients. This is a well documented problem for companies developing orphan drugs for the US market, as the population of patients suffering from any given rare disease is small.⁶⁶ In countries with populations that are smaller than that of the US (e.g. Canada), the logistical problems of conducting rigorous safety and efficacy trials are magnified, which will in turn make it exceedingly difficult for companies to recoup their development costs. While expanding the potential market by targeting patients in the US remains a possibility, developing a drug for the US is extremely expensive — a burden only large companies may be able to afford.⁶⁷

One potential enterprise that could help to lessen drug development costs, and hence lower drug prices, is the establishment of a Global Orphan Drug Office, along the lines of the comprehensive international policy proposed by Reider.⁶⁸ Such an office could consolidate individual orphan drug offices and be charged with the responsibility of overseeing international orphan drug development. Similar to the EU’s EMEA, a single office would significantly reduce costs for companies since they would only need to submit one application as opposed to several at present, and for countries since they would not need to maintain their own orphan drug offices. The development of orphan drugs on an international scale is also reasonable because it immediately mitigates the major obstacle to drug development — market size; both in terms of having an adequately sized patient pool to conduct rigorous clinical trials and having a large enough market to allow companies to recoup their investments. An ancillary benefit may be lower product

⁶⁵ *Supra* note 11 at 83.

⁶⁶ *Supra* note 1 at 823; Reider, *supra* note 10 at 299.

⁶⁷ “Safety in Numbers”, *supra* note 25 at 64.

⁶⁸ Reider, *supra* note 10 at 299.

prices for patients. Moreover, a global office could help companies accelerate clinical trials by identifying patients with specific rare diseases worldwide. This would also benefit rare disease sufferers because they could gain access to orphan drugs they might otherwise not be aware of by enrolling in an international clinical trial.

Any global office would require member countries to relinquish some control. This may not be a simple task given the considerable influence that the FDA and the US Office of Rare Diseases wield. However, history has shown that governments have submitted to public lobbying involving rare diseases. Thus, given enough pressure, a global office may be achievable. At the very least, if a Global Orphan Drug Office is not feasible, perhaps an agreement between each country with orphan drug legislation can be forged whereby a drug receiving orphan status in one country is automatically granted the same status in another country (a mutual recognition policy) — similar to the US-Australia agreement on orphan drugs.

7.2 Sales Triggers

While the institution of ODA reforms has been repeatedly turned down, the idea of a “sales trigger” specifically is promising. With some revision, an incentives structure incorporating a sales trigger may be amenable to the pharmaceutical industry. Instead of setting a single target sales figure for all orphan drugs, it may be possible for sponsor companies and the regulatory agency to negotiate different sales limits based on individual orphan drugs, or even therapeutic classes. The sales trigger approach in general benefits rare disease sufferers because even if companies insist on maintaining high prices, the sales limit will be reached sooner, meaning that the drug’s period of market exclusivity will expire earlier, opening up the market to competition and exerting negative price pressure. Alternatively, companies could maintain exclusivity by reducing the cost of the drug so that it will take longer to trigger the sales limit.⁶⁹ In either case, the consumer benefits because prices will eventually be reduced. By extending the opportunity to negotiate sales targets, the pharmaceutical industry may see this as a reasonable compromise because it allows companies to be involved in the process of setting the sales trigger limit, without having to disclose sensitive financial information.

7.3 Volunteerism

A coordinated approach to the problem by industry and governments of both developed and developing countries will likely be necessary to make any significant gains with respect to drug development for tropical diseases. Volunteer organizations such as Médecins Sans Frontières (MSF) have demonstrated that an initiative centered on volunteers can be effective in rebuilding and promoting health structures in developing countries. Perhaps a similar approach can be applied to drug

⁶⁹Reider, *supra* note 10 at 298.

development for tropical diseases. Developed countries, corporations, and philanthropic institutions could provide seed money to establish a not-for-profit organization focused on developing drugs for tropical diseases plaguing developing countries. With the support of their respective companies, researchers could volunteer their services for extended terms (i.e. six-months, one-year, etc.) and work on a project of their choosing so long as it addresses a tropical disease issue. At the end of a term, another researcher could continue the project. In time, such a venture could produce importantly needed drug neglected diseases and possibly even generate enough revenue to become self-sustaining.

In the process of searching for the next blockbuster drug, pharmaceutical companies screen thousands of molecules for potential therapeutic applications. Many promising molecules are shelved due to a limited predicted profitability. Instead of discarding a molecule that may have potential efficacy against a tropical disease, companies could donate the molecule to the volunteer organization for further investigation into its development potential.⁷⁰

Such an endeavor undoubtedly involves significant hurdles, especially when financial considerations are at the forefront. However, given time, a not-for-profit drug development venture based on volunteerism, could foster an environment where such humanitarian work is viewed as a positive within the research community.

8.0 Final Perspectives

While imperfect, the US ODA has been undeniably successful in fulfilling part of its original mandate. Given the changing landscape for drug development, reforms are required to bring the ODA back into line with its original intent. Since scientific advances like pharmacogenomics and increasingly complicated treatments will continue to inflate orphan drug prices, action will be required before costs prohibit access to potentially life-saving treatments for rare disease sufferers. The EU and Japanese orphan drug policies both incorporate measures to control drug prices. However, if any significant change in pricing practices are to occur, it will have to be initiated by the US due to the sheer size of their market and because the bulk of drug research and development occurs in that country.

While generous incentives are presently in place to promote the research and development of drugs for rare diseases, issues surrounding drug access need to be addressed. There is no point in creating incentives for the development of new drug therapies if population groups that need them, do not have access to them. With respect to Canada, lack of awareness about rare diseases and the high cost of orphan drugs have been identified as barriers to access. Rather than fund initiatives involving rare disease treatment research, efforts should be initially focused on improving therapy for rare disease sufferers, including rare disease diagnosis and

⁷⁰ *Supra* note 16 at 116.

access to treatments, by providing a central rare disease database and establishing a financial aid program to help patients procure orphan drugs.

Tropical, or neglected, diseases in developing countries have been shown to share similarities to rare diseases in developed countries — the lack of treatment options. While lowering drug costs and providing financial aid are some of the strategies employed to facilitate drug access for available treatment options, a more permanent, innovative, and sustainable initiative is required if any significant improvement in drug development for tropical diseases is to be attained.